En attendant, je m'en tiendrai à cette hypothèse que nous avons affaire à une anémie à type pernicieux constatée chez un enfant de 9 mois, sans que j'ose dans l'état actuel de la question établir le diagnostic d'anémie pernicieuse tout court.

## Résumé.

L'auteur réfère un cas d'anémie à type pernicieux chez un enfant qui, lors de la première examination, avait 9 mois. L'enfant est resté sous observation jusqu'à ce moment où il a trois ans, et au cours de ce temps il a eu à quatre reprises des symptômes d'une anémie grave, normohyperchrome, qui est restée réfractaire au traitement martial tout en réagissant à chaque fois avec la même promptitude à l'administration d'extrait de foie, avec une augmentation du chiffre des réticulocytes et amélioration des valeurs hématologiques. Des ponctions de la moelle osseuse montrèrent une moelle mégaloblaste caractérisée se changeant en moelle macro-normoblaste après traitement hépatique.

Après un bref aperçu des diverses formes d'anémie de la première enfance, l'auteur discute la diagnose à établir dans le cas référé. Celle d'anémie pernicieuse pouvant difficilement être posée à cause de l'âge du malade, l'auteur s'arrête à la diagnose d'anemie à type pernicieux. Il est probable que l'affection se soit déclarée par suite d'une réaction abnorme de la moelle osseuse à l'occasion d'infections répétées. Ajoute' pendant la correction des epreuves:

L'enfant de nouveau hospitalisé le 15.4.42. Nouvelle rechute, cette foisci sans infektion prealable.

Apres cette nouvelle rechute l'auteur ne croit plus de voir hesiter à diagnostiquer *une anemie pernicieuse* dont les premieres signes ont été constatés lorsque l'enfant en question n'avez que neuf mois.

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# ACTA MEDICA SCANDINAVICA

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bei denen zwar das Trauma nicht das die ersten Krankheitssymptome auslösende Moment gewesen zu sein scheint, wo aber die Gewalteinwirkung doch das sich später entwickelnde Krankheitsbild beeinflusst hat, indem es durch die Schaffung eines locus minoris resistentiae die Fortsetzung des krankhaften Prozesses in dem von der Gewalteinwirkung betroffenen Gelenk fixierte. So war es in dem folgenden Falle.

*N. H. S. Textilarbeiter. 30 Jahre.* Der Patient erkrankte *mit 29 Jahren* an typischer *chronischer rheumatischer Polyarthritis*, die mehrere Extremitätengelenke befiel, und gesundete allmählich nach etwa einem halben Jahr.

*Ein Jahr später verunglückte der Mann bei der Arbeit: beim Beladen eines Lastkraftwagens fiel er aus etwa 2 m Höhe auf einen Haufen Ketten und stiess beim Aufprall mit grosser Wucht den linken Ellenbogen in die Ketten. Am folgenden schwoll das linke Ellenbogengelenk* so stark an, dass der Mann das Hemd nicht darüberziehen konnte, gleichzeitig bekam er *Fieber*, 38.7°. Bettruhe. Nach 2 Tagen ging er zum Arzt, welcher feststellte, der Patient habe ein *Rezidiv seiner chronischen rheumatischen Polyarthritis* bekommen und wies ihn in die hiesige Rheuma-Klinik ein, wo im Laufe der Behandlung ein typisches chronisches rheumatisches Polyarthritissyndrom festgestellt wurde, und *zwar hatte dieses einen besonders malignen Charakter mit Knochen- und Knorpeldestruktion sowie nachfolgenden leichteren reaktiven Veränderungen in dem früher durch Gewalteinwirkung verletzten linken Ellbogengelenk*, das auch erst später von dem arthritischen Prozess frei wurde, als die übrigen angegriffenen Glieder. Es blieb ein Extensionsdefekt von 15° des linken Ellbogengelenks zurück.

In diesem Falle war das Trauma das direkt auslösende Moment eines Rezidivs der rheumatischen Infektion des Patienten, die pathologische Konstitution des Patienten aber war in diesem Falle daraus zu ersehen, dass er schon früher ein Polyarthritissyndrom gehabt hatte, das damals nicht durch äussere Gewalt ausgelöst worden war. Aber auch in dem hier vorliegenden Falle schuf das Trauma ein locus minoris resistentiae, das den rheumatischen Prozess fixierte und ihm an dieser Stelle einen besonders malignen und destruktiven Typus verlieh.

Wie es kommt, dass die Arthritis in dem früher von äusserer Gewalteinwirkung getroffenen Gelenk, auch wenn sie ursprünglich eine benignere Synovitis ist, doch leicht allmählich einen destruktiveren Charakter annimmt, ist u. a. von Bick klargestellt worden. Dieser hat nämlich durch Experimente an allergisierten Tieren, bei denen man die hyperergischen Arthritiden in der Weise

HELSINGFORS 1942
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kaudal von $C_4$ ab ihre lordotische Form zu verlieren und in kranial-ventraler Richtung gerade zu werden. Dauerte die Belastung noch länger, wurde die Wirbelsäule innerhalb der beschriebenen Partie schwach kyphotisch, d.h. sie nahm eine Form an wie bei maximaler Ventralbeugung. Oberhalb $C_4$ resultierte indessen rein kompensatorisch eine Steigerung der Lordose, um den Kopf in Normal-



Fig. 7. Dieselbe Versuchsperson wie in Fig. 6 nach Kopfbelastung von 12 kg während ca 4 Minuten.

stellung behalten zu können (s. Fig. 6 u. 7). Während der Belastungsdauer empfanden die Versuchspersonen stets Müdigkeit im unteren und mittleren Teil des Halses. Bei fortgesetzter Belastung ging dieses Gefühl in mässigen Schmerz über. Zuweilen wurde erklärt, dass der Schmerz zum Hinterkopf hinaufstrahlte. Bei Palpation, nach Schluss der Belastung, war beiderseits der Spinalfortsätze, innerhalb der beschriebenen Gegend, leichte Schmerzhaftigkeit vorhanden. Nach beendeter Belastung verharrte die Halswirbelsäule in der pathologischen Stellung während einer halben

# INDEX.

## Vol. CXI.


Pag.

*N. I. Nissen, H. C. Engbaek* and *H. Buch* (Copenhagen): Sulfathiazol and sulfamethylthiazol in the treatment of pneumonia ..... 1

*K. Malthe Jacobsen* (Svendborg, Dänemark): Reticuloendotheliose-Monozytenleukose ..... 30

*Jens Bing* and *Axel V. Neel* (Copenhagen): On the site of production of pathologically increased globulin as elucidated by conditions in cerebrospinal fluid ..... 57

*Gunnar Nielsen* (Aarhus, Denmark): Heparin and the blood sedimentation reaction ..... 66

*Svend Petri, Hans Jensenius, Flemming Norgaard* and *Erik Thyssen* (Copenhagen): Experimental studies on production of pernicious anemia by operation on the digestive tract. 4. Results of extensive resection of the distal part of the small intestine (on pups) ..... 75

*Jens Dedichen* (Oslo): Anémie à type pernicieux chez un enfant de 9 mois. 90

*Torben Jersild* and *Kurt Iversen* (Aalborg, Denmark): Erythema nodosum arising from treatment with sulfathiazole ..... 105

*Svend Petri, Hans Jensenius, Flemming Norgaard and Erik Thyssen* (Copenhagen): Experimental studies on production of pernicious anemia by operation on the digestive tract. 5. Results of extensive resection of the proximal part of the small intestine (on pups) ..... 116

*Torben Jersild* (Aalborg, Denmark): Parotitis meningitis with special reference to cases without swelling of the parotid gland..... 123

*Gunnar Edström* (Lund, Schweden): Klinische Studien über den chronischen Gelenkrheumatismus. III. Die prodromalen Krankheitsbilder ..... 137

*Gunnar Edström* (Lund, Schweden): Klinische Studien über den chronischen Gelenkrheumatismus. IV. Trauma und Rheumatismus..... 150

*Bo-Eric Ingelmark* (Upsala, Schweden): Über schmerzhafte Insuffizienszustände im Halse ..... 172

*Kaj Roholm* and *Gunnar Teilum* (Copenhagen): Feminizing tumors of the suprarenal cortex, with description of a case ..... 190

*F. Gerritzen* (Lunteren, Holland): The 24-hours' rhythm in diabetes ..... 212

*K. A. Ekbom* (Stockholm): Quinine in extrapyramidal morbid conditions.. 221

*Erik Trier* (Gentofte, Denmark): The hepatorenal syndrome ..... 236

*Ernst Bárány* (Upsala, Sweden): On the mechanical impedance of the human thorax ..... 252

*Egon Bruun* and *Knud Hermann* (Copenhagen): Polyneuritis after treatment with sulfonamide preparations ..... 261

*Fritz Schonheyder* and *Axel Olsen* (Aarhus, Denmark): On the prothrombin content in blood at parturition ..... 280

*Jens Bang* (Copenhagen): Experiments with the transfer of infectious mononucleosis to monkeys (macacus rhesus) — with negative results..... 291

*Einar Hollström* (Upsala, Sweden): Some observations on the morphology of the tubercle micro-organism with special regard to its mycotic nature.. 303

*H. C. A. Lassen* (Copenhagen): Chemotherapy in meningococcal meningitis 310

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Pag.

*Gunnar Dahlberg* (Upsala, Sweden): The occurrence of alcoholics and their treatment ..... 325
*H. W. Scalongne* (Rotterdam, Holland): Über den normalen Vitamin A-Blutspiegel ..... 359
*F. L. J. Jordan* (Utrecht, The Netherlands): Clinical investigations about complement ..... 372
*H. Venndt and P. Plum* (Copenhagen): Investigations into the cause of the physiological hypoprothrombinemia in new-born children. I. Investigations into the bile acid production in new-born infants ..... 396
*Marie R. H. Stoppelman* (Amsterdam): The influence of synthetical vitamin upon the agglutinating power of serum ..... 408
*A. W. M. Pompen* und *R. Ruiter* (Deventer, Holland): Beitrag zu der Differentialdiagnose der erythrodermischen Form der Hodgkinschen Krankheit ..... 414
*H. Rasmussen* and *M. Foss* (Oslo): The electrocardiogram of acute hemorrhage from stomach and intestines ..... 420
*Edgar Mannheimer* (Stockholm): The interpretation and significance of the various types of gallop rhythm ..... 442
*M. Weiss* (Upsala, Schweden): Über Albumosurie im gesunden und kranken Organismus ..... 457
*Kaj Larsen* and *Pélur Magnusson* (Copenhagen): The abnormal electrocardiogram. I. Saddle-formed ST segments ..... 488
*Vagn Mortensen* (Copenhagen): Studies on the electrocardiographic diagnosis of acute and fibrous infarction of the heart, on the basis of 51 cases with autopsy. I. Introductory remarks. Solitary infarcts ..... 503
*Vagn Mortensen* (Copenhagen): Studies on the electrocardiographic diagnosis of acute and fibrous infarction of the heart, on the basis of 51 cases with autopsy. II. Multiple infarcts. Survey of the entire material ..... 518
*Sven Hammarström* and *Åke G. H. Lindgren* (Stockholm): Postural hypotension in a patient with multiple encephalomalacias ..... 537
*Maj-Lis Åberg* (Helsingfors): The reticulocytes at the formation of rouleaux and the sedimentation reaction ..... 555
Volumes supplémentaires des Acta medica scandinavica publiés 1921—1942 566

Revue des livres:

*I. Holmgren:* C. Heinemann-Grüder und E. Rühe: Der Arzt in der Wehrmachtversorgung ..... 219
*I. Holmgren:* Hans Käfer: Feldchirurgie ..... 220

---

Supplementum CXXXIII, *Per Wising* (Stockholm): A study of infectious mononucleosis (Pfeiffer's disease) from the etiological point of view.

Supplementum CXXXIV, *Jørgen E. Thygesen* (Copenhagen): The mechanism of blood sedimentation.

Supplementum CXXXV, *Erik Hedvall* (Upsala, Sweden): Bovine tuberculosis in man. A clinical study of bovine tuberculosis, especially pulmonary tuberculosis, in the southernmost part of Sweden, and *Hilding Magnusson* (Malmö, Sweden): The relation between bovine and human tuberculosis from the veterinary point of view.

Supplementum CXXXVI, *Paavo Maijala* (Helsingfors): Klinische Untersuchungen über die Häufigkeit und Art der seropositiven Spätlues in Finnland.

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3000 M. U. of estrine per liter of urine and a slight increase in androgenic hormone (> 50 < 100 cock's comb units). The Aschheim-Zondeks reaction was negative in June 1935, and January 1936. Analysis of the morning urine voided on the day of the operation (July 1931) showed no gonadotropic hormone (Burrows and collaborators).

## Discussion.

The symptoms in the 7 published cases of feminizing cortical carcinoma of the suprarenal are recorded schematically in Table 3. In several of these cases the data are incomplete. Thus information about the condition and function of the genitals is wanting in the cases reported by Parkes Weber and by Lisser. In all 7 cases the tumor was examined either on autopsy or operation, and its relation to the suprarenal was established. Previously microscopy of the breasts was performed only twice (Bittorf, Parkes Weber), of the testes only once (Bittorf). A thorough autopsy has been reported only in our case.

Notwithstanding the incomplete data it is obvious that cortical carcinoma in mature men in rare cases is accompanied by symptoms from the genital system, namely: gynecomasty, genital atrophy and loss of the sexual function. These phenomena were present in 4 of the best examined cases. Holl states that in one of his patients (the 15-years-old boy) the genitals were normal, it is true, but this fact as well as the slight gynecomasty are probably explained by the unusually rapid course of the disease, only a few months passing between the recognition of the tumor and exitus. Moreover, an important symptom, demonstrated in the two last described cases, is a very considerable increase in the estrogenic hormone content of the urine together with a more moderate increase in the amount of androgenic substances. In their patient Levy Simpson & Joll found a maximum of > 3000 M. U. of estrine and 50—100 C. C. U. of andrine per liter of urine. Our patient excreted up to about 5000 M. U. of estrine and 50—80 C. C. U. of andrine per 24 hours.

On histological examination the breasts show fibrosis with some lumina of mammary glands here and there. In our case the testes were quite atrophic, with loss of tubular epithelium as well as interstitial tissue. The hypophysis showed some fibrosis but no change in the proportion between the normal cell forms.

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From Department E (Infectious Diseases), the Frederiksberg Hospital, Copenhagen.
(Chief Physician: N. I. Nissen, M. D.)

# Sulfathiazol and sulfamethylthiazol in the treatment of pneumonia.

## Toxic Complications, especially Neuritis.

By

N. I. NISSEN, H. C. ENGBÆK and H. BUCH.

(Submitted for publication January 19, 1942).

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In a previous paper (8) we have reviewed the literature concerning the clinical serviceability of sulfathiazol and sulfamethylthiazol and at the same time presented a pneumonia material comprising 75 patients treated with sulfamethylthiazol, besides some studies on the concentration of this substance in the blood and urine. After the conclusion of this therapeutic series we have now looked into the employment of sulfathiazol along the same lines. Thorough studies, especially comparative, on the effect and toxic symptoms produced by these two remedies seemed highly desirable on account of the increasing, often uncritical employment of these new preparations, and also because the toxic complications associated with the employment hitherto have received but slight attention, at any rate, in this country.

*Material.* — All the pneumonic patients admitted to this department during the period of 1/3—1/10, 1941, altogether 92 patients, were treated with sulfathiazol (Ferrosan's preparation »Chemosept»), a few of them also with sulfapyridine, M & B 693, or with antipneumococcus serum. These patients are recorded in Table 1 in

with impairment of renal function, Brit. med. J. 1941: 1: 427. — Dérot, M. & R. Dérot-Piquet: Les Hépatonéphrites, Paris 1937. — Dudley, S. F.: Toxic nephritis following exposure to carbon tetrachloride and smoke fumes, J. Indust. Hyg. 1935: 17: 93. — Fishberg, A. M.: Hypertension and Nephritis, London 1939. — Husfelt, E. & T. Bjering: Nyrebeskadigelse ved traumatisk choc, Hospitalstid. 1935: 78: 781. — Iversen, P., T. Bjering & J. Bing: De medicinske Nyrelidelser, Kobenhavn 1941. — Kaijser, R.: Über sog. hypochlorämische Reststickstoffsteigerung, Upsala Läkaref. Förh. 1940—41: 46: 109. — Mayon-White, R. & O. M. Solandt: A case of limb compression ending fatally in uremia, Brit. med. J. 1941: 1: 434. — Moller, K. O.: Some cases of carbon tetrachloride poisoning, etc., J. Indust. Hyg. 1933: 15: 418. — Nonnenbruch, W.: Das hepatorenale Syndrom, Verhandl. d. deutsch. Gesellsch. f. inn. Med. 1939: 341. — Nonnenbruch, W.: Über das hepatorenale Syndrom bei der Stauungsleber Herzkranker und seine Beeinflussung durch Salyrgan, Deutsches Arch. f. klin. Med. 1941: 187: 465. — Pasteur-Vallery-Radot, G. Mauric & A. Domart: Un cas de néphrite aigué d'allure grave par inhalation de tétrachlorure de carbone, Bull. et mém. Soc. méd. d. hôp. de Paris 1938: 803. — Romeling, T.: Dodelig Tetraklorkulstofforgiftning, Ugesk. f. Læger 1940: 102: 337. — Schütz, H.: Über ein hepatorenales Syndrom bei Tetrachlorkohlenstoff-Vergiftung, Arch. f. Gewerbepath. u. Gewerbehyg. 1938: 8: 469. — Simon, M. A.: Acute toxic nephritis due to inhalation of carbon tetrachloride fumes, Canad. M. A. J. 1939: 80: 580. — Smetana, H.: Nephrosis due to carbon tetrachloride, Arch. Int. Med. 1939: 63: 760. — Thompson jr., L. L., W. D. Frazier & I. S. Rawdin: The renal lesion in obstructive jaundice, Am. J. M. Sc. 1940: 199: 305. — Vague, J.: Les Hépatonéphrites aiguës. Paris 1935. — Vollhard, F.: Bergmann-Staehelins Handbuch der Inneren Medizin, 6. Band. Berlin 1931.

the same manner as the patients in the above-mentioned sulfamethylthiazol material. In Tables 2 and 3, for the sake of comparison, the age and pneumococcal type distribution of the patients is given respectively for the sulfathiazol and the sulfamethylthiazol materials.

*Technique of Examination and Dosage.* — We have used the same methods for examination and estimation of the pneumonic cases and the same dosage and therapeutic technique as mentioned in the paper on the sulfamethylthiazol therapy (Acta med. Scandinav. 109: 417, 1942).

*Therapeutic Results.* — A thorough comparison of the sulfamethylthiazol and sulfathiazol materials showed on the whole no particular difference for the two groups of patients. Still, the sulfathiazol material comprises several more old patients than does the sulfamethylthiazol group. On the other hand, the latter is a winter material. In general, both groups of patients represent a pneumonia material of moderate severity. In the sulfamethylthiazol material there was only one case of bacteriemia, in the sulfathiazol material there was no such instance.

Of the sulfathiazol-treated patients 10 died, that is, 10.9 %.

*Patient No. 2* was strongly intoxicated on admission to the hospital, and no effect on the temperature was obtained in 24 hours. Autopsy revealed apical pneumonia, meningeal irritation and small cerebral hemorrhages (spinal fluid cultures: no growth).

*No. 13* was very exhausted from whooping-cough which had lasted 14 days. Within 24 hours there appeared a nice fall in the temperature, but then the temperature suddenly increased again to hyperpyrexia, and the patient died 2 ½ days after the institution of treatment. (N. B.: Good diuresis; no hematuria.) Autopsy showed extensive pneumonic processes; no lesion of the urinary passages. The secondary rise in temperature can hardly be attributable to medicamental allergy, for which it appeared too early; but it may be ascribable to cerebral intoxication (brain not examined).

*No. 49* had been confined to bed at home for 7 days with continuous fever and symptoms of influenza. On admission the patient was exhausted and cyanotic, with beginning pneumonia in the lower part of the right lung. Blood examination showed relative leucopenia; white blood count, 5440; no shift in the Arneth blood picture to the left. The chemotherapy showed no effect on the temperature

tion, whereas, in the latter case, provided it were possible to induce the inebriate to keep sober, he would be a normal citizen. Owing to abuse of alcohol, he is unfit and degraded socially.

In order that intervention may take place by the Temperance Board with regard to a drunkard, he must, according to current regulations, be addicted to abuse of alcohol, either continuously or for long periods. Furthermore, before 1930, internment could only be enforced when the person in question 1) was a source of mortal danger to himself and to others, 2) exposed his family to neglect or destitution, or was dependent on public assistance or support from relatives, or 3) had been convicted for drunkenness repeatedly for the last two years. After the year 1931, additional stipulations have been in force, i. e. after that time an inebriate might be interned also when 4) he is a disturbance to his neighbours and, 5), when he is incapable of taking care of himself.

Thus, generally speaking, the poor benefit by the law in so far as they may, to a greater extent, be taken care of by the Board. A person who is well-to-do and a habitual drunkard, of course, need not land in a position where he is compelled to resort to the authorities for support. His family does not have to be subjected to destitution because he has been dismissed from his work on account of drunkenness, etc. A well-off person can take a car home from the public house when he is intoxicated and, consequently, does not run the same risk as the poor man of being arrested by the police and convicted for drunkenness. *Inter alia*, the additional stipulations have served the purpose of facilitating intervention more frequently with regard to rich people. Nevertheless, it is apparent that even these stipulations have not achieved equality. Well-to-do persons are taken care of at private institutions. Accordingly, they are not reported to the Temperance Board as they can afford to pay for their treatment. Still, the existence of temperance boards has not been a matter of indifference to the wealthy alcoholics. If they did not voluntarily consent to internment, they could be told that compulsory detention would be enforced.

This side of the question has been treated rather extensively, in order to emphasize the fairly small extent to which the alcoholics from the upper classes have been included in the material. Thus, the figures obtained concerning the occurrence of alcoholism are minimum figures. Furthermore, the fact should be set down that

einen höheren Vitamin A-Blutspiegel haben sollten. Auch ich selber fand in früherer Arbeit (34) dass ein Vitamin A-Gehalt von mehr als 8 I. E. nur ausnahmsweise gefunden wird.

Tabelle I gibt eine Übersicht von 78 Vitamin A Bestimmungen, ausgeführt in Oktober/November 1939 und Februar/März 1940. Alle untersuchte Personen wohnten in Rotterdam, ihr Alter wechselte von 20—55 Jahren. Sie fühlten sich ganz gesund, standen nicht unter ärztlicher Behandlung und ihre Blutkörperchensenkungsgeschwindigkeit war niemals höher als 20 mm nach einer Stunde. Keine der untersuchten Frauen war schwanger, stillend oder in der Menopause. Es wurden immer Ehepaare untersucht, von denen feststand dass sie mindestens in den letzten 14 Tagen vor der Untersuchung die gleiche Nahrung zu sich genommen hatten. Diese Ehepaare waren die gesunden Eltern von Kindern die im Krankenhause gepflegt wurden wegen Hernien, Vergiftungen oder Traumen. Beim Aufnehmen der Ernährungsanamnese der zu untersuchenden Personen wurde besonders die Art von Butter die die Familie gebrauchte beachtet: nichtvitaminisiertes Margarin, vitaminisiertes Margarin oder Sahnenbutter. Der grösste Teil der untersuchten Ehepaare gehörte zu der Bevölkerungsgruppe der Arbeitslosen, ein Teil gehörte zu der Arbeiterklasse und es fanden sich unter ihnen auch einige die zum Stande der kleinen Beamteten gehörten. Bei allen untersuchten Personen wurde das Blut nüchtern um ungefähr 9 Uhr im Morgen aus der gestauten Armvene abgenommen. Bei der Gruppierung nach der gebrauchten Art von Butter, wie diese in Tabelle I vorgenommen wurde, ist zu beachten dass die Gruppe die vitaminisiertes Margarin gebrauchte überwiegend aus Arbeitslosen bestand (diese Art von Margarin wurde von der Behörde an Arbeitslosen verabreicht). Die Personen aus den beiden anderen Gruppen leben gewöhnlich in etwas besseren sozialen Verhältnissen.

Viele Ärzte die bei Verdacht auf Vitamin A Mangel eine Vitamin A-Bestimmung verrichten lassen, meinen (nach dem Schema von Wolff) wenn Werte von 6—7 I. E. gefunden werden, dass sie mit einem »mässigen« Gehalt an Vitamin A oder gar mit einer Defizienz zu tun haben, indem Untersucher die auf diesem Gebiete mehr Erfahrung haben wissen dass diese Werte eigentlich die Regel sind. Es liegt auf der Hand dass dieses zu falschen Auffassungen und auch zu falscher Therapie führen kann. Ein eingehendes Studium des normalen Vitamin A-Gehaltes im Blute ist dann auch nicht überflüssig.

Wolff kam zu seiner Annahme durch die Wahrnehmung dass gutsituierte Personen regelmässig einen Vitamin A-Blutspiegel von mehr als 8 I. E. hatten, im Gegensatz zu kleinen Beamteten und Arbeitern. Wolff hat sich also als Norm das Verhalten bei

The alterations in the electrocardiogram during hemorrhage resemble, as stated, those seen in myocardial anoxemia, induced, for example, by angina pectoris or by breathing air poor in oxygen. As has been shown, the concentration of hemoglobin in the blood is of no significance for the occurrence of the changes, and as a rule there is no fall in blood pressure, but rather the reverse. If it is a fact that the electrocardiographic abnormalities are due to myocardial anoxemia, it then seems necessary to conclude that a *coronary spasm* is present in these individuals with normal hearts. Many investigations, especially of experimental nature, seem to show that in acute hemorrhages reactive vascular spasms occur in the periphery, in arteries and in arterioles, because the capacity of the vascular system must necessarily be immediately adjusted to the reduced blood volume. The electrocardiographic changes found might then be taken to indicate that such reactive arterial spasms arise not only in the periphery, but also centrally, in the vessels of the cardiac muscle itself. Whether this is salutary or deleterious is another question. The pathogenesis of the electrocardiographic changes in dehydration with extrarenal hyperazotemia and in diabetic coma is not known with certainty. But we know that a reduction of the blood volume takes place in these conditions, and the possibility then exists that reactive arterial spasms arise here, in order that the capacity of the vascular system may be adapted to the reduced blood volume. In case of dehydration, however, a fall in blood pressure and a reduced velocity of blood flow come into play as factors which render the coronary circulation still more difficult. In case of the orthostatic changes in the electrocardiogram the fall in blood pressure also seems to be of essential importance, and the common explanation of the orthostatic electrocardiogram seems to be that it is due to myocardial anoxemia. Nordenfelt's (10) interpretation of the orthostatic electrocardiogram as being an indication of increased sympatheticotonia shall here merely be mentioned. As already stated, the electrocardiograms of hemorrhage show no special tendency to high P waves in any of the leads and neither is tachycardia present. Nordenfelt's contestion that increased sympathicotonia leads to reduced height and inversion of the T waves is in conflict with the view, commonly held and especially based upon Rothberger's works (12). Nordenfelt does not seem to supply

**Table 2.**

*Age Distribution of Pneumonic Patients Treated with Sulfamethylthiazol or Sulfathiazol.*

| Age (years) | No. of pts. treated with sulfamethylthiazol | with No. of death | No. of pts. treated with sulfathiazol | with No. of death |
|---|---|---|---|---|
| 0— 1 | 5 | 1 | 7 | 1 |
| 2— 5 | 9 | 0 | 16 | 1 |
| 6—14 | 7 | 0 | 13 | 0 |
| 15—25 | 13 | 0 | 12 | 0 |
| 26—45 | 19 | 1 | 11 | 1 |
| 46—60 | 10 | 1 | 11 | 2 |
| 60 | 12 | 3 | 22 | 5 |
| | 75 | 6 = 8 % | 92 | 10 = 10.9 % |

for 48 hours; then there was a sudden fall in temperature to subnormal values. 4 days after institution of treatment, microscopic hematuria was demonstrated; and the sulfathiazol treatment was discontinued. Then the temperature rose again, and an exudative pleurisy developed. Suddenly the temperature rose rapidly to hyperexia, and the patient died. Intravenous chemotherapy ante mortem showed no effect. The blood picture showed no sign of agranulocytosis. Autopsy: Influenza, pneumonia with signs of severe cerebral irritation, with oedema of the brain and hemorrhages.

*No. 62*, an obese patient with electrocardiographic and clinical symptoms of myocardial degeneration, entered the hospital in a very exhausted state, with pneumonia involving the entire left lung. The treatment had a favorable initial effect, but on the 4th day of treatment there was again a rise in temperature, accompanied by signs of pleurisy, and now the chemotherapy had no effect. Hence the patient was given antipneumococcus serum which resulted in a moderate fall in temperature. There was a transitory serum rash. Now the electrocardiograms showed additional severe changes, with the T-waves missing in all leads and numerous extrasystoles. The patient died on the 18' day of illness with features of sepsis (the blood cultures were constantly negative). The blood picture showed relative leucopenia, with only a slight shift to the left in the Arneth blood picture. No autopsy.

*No. 65.* Type 3 pneumonia, with oedema of the lungs. No definite effect from chemotherapy; careful general treatment. The

teristic electrocardiographic abnormalities. The negative result may be due to the hemorrhage being too small, and further to the fact that women in pregnancy and puerpery, through their increased blood volume and perhaps also through other mechanisms are specially protected against the effects of such hemorrhages. We have not yet had occasion to investigate sufficiently thoroughly the conditions in other forms of copious external hemorrhages.

## Discussion.

On systematic investigation of the electrocardiogram in patients with gastro-intestinal hemorrhage it was found that the first, incidentally observed case was not an exceptional occurrence. Characteristic abnormalities, in the ST interval and the T wave, are frequently arising consequences of such hemorrhages. The frequency of these alterations during hemorrhage may be estimated at almost 50 per cent, but it is probable that a more minute examination would yield still higher figures.

The various stages of ST anf T abnormalities, from flattening of the T wave, often with tent-shaped peaks, to isoelectric and deeply inverted T waves, have been observed either in different patients or as phases of development that can be followed from day to day in one and the same patient. It therefore seems justifiable to regard this electrocardiogram of acute hemorrhage as a new electrocardiographic syndrome, on a line with other functional and transient electrocardiographic syndromes, such as the orthostatic electrocardiogram, the electrocardiogram of angina pectoris, of pulmonary embolism, etc.

Occasional examples of such electrocardiograms of hemorrhage have earlier been observed. Aschenbrenner (1) has reported a single case, which, however, has been regarded with considerable doubt, partly because his patient had only insignificant anemia, partly because the patient was stated to have previously had »myocardial weakness» and also because he was treated with strophantin. Particularly on going through the literature about the electrocardiogram in anemia we can find undoubtable cases with such electrocardiograms, as well as cases which can with great probability be assigned to that group. Bloch's Case No. 53 (4)

**Table 3.**

*Distribution of Pneumococcus Types in Patients Treated with Sulfamethylthiazol (SMT) or Sulfathiazol (ST).*

| Pneumococcus types | Lobar pneumonia | | Lobar + bronchopn. | | Broncho-pneumonia | | Total pts. treated | | Total dead |
|---|---|---|---|---|---|---|---|---|---|
| | SMT | ST | SMT | ST | SMT | ST | SMT | ST | |
| 1 | 6 | 7 | | | | | 6 | 7 | |
| 2 | 3 | 4 | 1 | | | | 4 | 4 | |
| 3 and 3 + 8 | 3 | 4 | 5 | 1 | 1 | 1 | 9 | 6 | 3 |
| 4 | 2 | | | | | 1 | 2 | 1 | |
| 5 | | 1 | | 1 | | 1 | 2 | 1 | |
| 6 and 6 + other types | 3 | 1 | 3 | 2 | 1 | 4 | 7 | 4 | 1 |
| 7 | 2 | 5 | | | | | 2 | 5 | 1 |
| 8 and 8 + 33 | 2 | 1 | | 3 | | 1 | 2 | 5 | 3 |
| 9 | | 1 | 3 | | | | 3 | 1 | 1 |
| 12 | 1 | 3 | | | | | 1 | 3 | |
| 14 | | | 2 | | | 1 | 2 | 1 | |
| 16 + 24 | | | | | | 1 | | | |
| 18 | | 1 | 2 | | | | 2 | 1 | |
| 19 and 19 + 21 | 4 | 3 | 1 | 4 | 2 | 1 | 7 | 8 | 2 |
| 20 | | | 1 | | 2 | | 3 | | 1 |
| 22 | | | | | | 1 | | 1 | |
| 23 | 1 | | 1 | 1 | | | 2 | 1 | |
| 29 | | 1 | | | | | | 1 | |
| 31 | 2 | | 1 | | | | 3 | | |
| 32 | 1 | 1 | | | | | 1 | 1 | |
| 34 | | 1 | | | | | | 1 | |
| 35 | 1 | | | | | | 1 | | |
| No pneumococci | 9 | 20 | 7 | 6 | 2 | 8 | 18 | 34 | 2 |
| Not examined | | | | | | 1 | | 1 | 1 |
| Total | 40 | 54 | 27 | 18 | 8 | 20 | 75 | 92 | 15 |

sulfathiazol values in the blood varied from 13.4 to 16 mg %. There was marked leucocytosis, with a great shift to the left in the Arneth blood picture. Autopsy. Diffuse bronchopneumonia; myofibrosis and hypertrophy of the heart.

*No. 87.* Lesion complicated by severe myocardial degeneration + symptoms of insufficiency. Good effect from the chemotherapy, with fall in temperature to normal level. The patient died subsequently from infarction pneumonia after phlebitis.

sons), while no particular cause of the phenomenon could be demonstrated in the rest of the cases. For this reason, Van Nieuwenhuizen and collaborators assign no definite diagnostic significance to the saddle-formed ST segment, but they assert that the occurrence of saddle-formed ST segments calls for a very thorough examination of the heart, also in young persons.

While the above-mentioned investigators, including Kirchner, take saddle-formed ST segments to be a sign of commencing coronary sclerosis or of functional disturbances in the coronary arteries, Radnai looks upon the occurrence of saddle-formed ST segments as a sign of coronary thrombosis, threatening or already present. Radnai has never observed this anomaly in normal persons or in patients with other heart lesions; on the other hand, he found it in one year in 22 out of about 300 patients with coronary lesions. In 4 of these 22 patients coronary thrombosis made its appearance shortly after the examination; in 2 other patients this change in the electrocardiogram developed in the course of typical coronary thrombosis; and in one patient the anomaly turned up some time after the establishment of coronary thrombosis.

A few authors have questioned the diagnostic significance of the saddle-formed ST segments — for instance, Kaj Larsen & Skúlason who found saddle-formed ST segments in 22 out of 100 healthy persons aged from 30 to 50 years, and Eggers who found saddle-formed ST segments in 21 out of 100 young sportsmen.

### *Writers' Investigation.*

We designate the ST segment as saddle-formed when, after leaving the QRS complex, it takes the form of a downward convex curve going over into the positive T wave, without reaching 1 mm below the isoelectric line. ST segments which extend 1 mm or more below the isoelectric line are designated as negative.

Saddle-formed ST segments occur most often (see Table 3) after QRS complexes in which the S wave is absent. The descending limb of the R wave may gradually turn into the ST segment (Fig. 1A), or there may be a notch at the base of the descending limb of the R wave (Fig. 1B). Saddle-formed ST segments may occur, however, also after QRS complexes with a distinct S wave. In most of these cases (Table 3) the S wave will be followed by an

*No. 90.* Lesion complicated by severe myocardial degeneration with arrhythmia perpetua. Good effect from the chemotherapy, with fall in temperature to normal level. The patient died subsequently with increasing dementia and cardiac insufficiency.

*No. 85.* Lesion complicated by severe myocardial degeneration and arterosclerosis + pulmonary hypostasis. Good effect from the first series of sulfathiazol; no effect from the second series. The patient died probably of pulmonary embolism. No autopsy.

*No. 91.* No effect from the therapy. The patient died with increasing cardiac insufficiency and dementia.

*No. 92.* Same clinical picture as that of No. 90.

In spite of the unavoidable deaths among the old patients, the therapeutic result has been very fine. Properly, we think, the case mortality should perhaps be corrected to 5.5 by omitting the last-mentioned five fatal cases. For the sulfamethylthiazol material the corresponding figure would be 4.0. So the therapeutic result is the same for the two groups.

Nor is there any essential deviation in the form of the temperature curves for the two materials examined as described in our preceding paper. The observations made concerning the form of the temperature curves for the sulfamethylthiazol-treated patients, especially in relation to the sulfapyridinetreated patients, apply also to the sulfathiazol-treated: the effect on the temperature should appear early, preferably within 4—8 hours, and be less abrupt than in sulfapyridine therapy. Uncomplicated lobar pneumonia yields most promptly and completely; influenza pneumonia often responds poorly, and no better to sulfathiazol than to sulfapyridine.

*Thus, there is no demonstrable difference in the action or in the effect of sulfathiazol and sulfamethylthiazol.*

*Toxic Complications of Sulfathiazol Therapy.* — These complications are recorded in Table 4. For the sake of comparison, this table gives also the complications observed in our own sulfamethylthiazol material and in two foreign sulfamethylthiazoltreated patient materials.

Thus, in our material there was no instance of neuritis or psychosis, nor signs of severe morphological changes in the blood picture. The gastro-entestinal symptoms were very mild and did in no way interfere with the treatment. In the materials reported by Brown & Herrell and Berglund & Frisk too the complications were

27 a completely occluding thrombosis of the right coronary artery was described but no infarct of the posterior wall. The patient died shortly after the appearance of the occlusion, and presumably this case was of the same character as some cases in the first two groups, in which there was a fresh occlusion of the coronary artery but no infarction because of an early exitus. In 8 cases the autopsy revealed a fresh anterior wall infarct + a fibrous posterior wall infarct; in 3 cases there was a fibrous anterior wall infarction + a fresh infarct of the posterior wall; 6 cases showed fibrous infarction of the anterior wall + fibrous infarction of the posterior wall; 1 case presented the combination of fresh anterior wall infarction + fresh posterior wall infarction; and in 2 cases the nature of the infarcts could not be decided.

As to the anterior wall infarcts, in 13 cases they are described as occupying a part of the anterior wall, and the lower anterior part of the septum, in 5 cases only some part of the anterior wall (respectively »towards the apex», »lower ⅓», »middle of the anterior wall» or merely »the anterior wall» without any more precise data) and in 2 cases the description was vague. In 10 cases the posterior wall infarcts are described as located »in the posterior wall», in 2 cases »in the upper part of the posterior wall», in 2 cases »in the posterior wall + the posterior part of the septum», in 3 cases »in the lower part of the posterior wall + the posterior part of the septum», and in 2 cases the post-mortem description was vague.

In 13 cases the anterior descending branch and the right coronary artery were occluded, and in 5 of these the occlusion involved also the left circumflex branch. In 1 case the anterior descending branch and the left circumflex branch were occluded. In the remaining 6 cases the occlusion was described as involving the right coronary artery in 3, the anterior descending branch in 3, and associated with »marked sclerosis of the other arteries» in all 6 cases.

In the anterior descending branch the occlusion was found »just distally to the branching» in 3 cases, »in the upper part of the branch» in 2 cases, »1 cm from the branching» in 1 case, »2 cm from the branching» in 1 case, »2.5 cm from the branching» in 3 cases, »8 cm from the branching» in 1 case, »in the distal ⅓» in 2 cases, and in »the lower part» in 1 case. The right coronary artery was occluded »at the branching» in 2 cases, 3—4.5 cm from the branching in 3 cases, »at its bending on the posterior surface» in 1 case, »in its distal

**Table 4.**

*Medicamental Complications in the Writers' Materials and Complications Reported by Other Authors.*

| Materials and treatment. (Authors) | 92 patients treated with *sulfathiazol* (Nissen, Engbæk & Buch) | 75 patients treated with *sulfamethylthiazol* (Nissen, Engbæk & Buch) | 101 patients treated with *sulfamethylthiazol* (Brown & Herrell) | 64 patients treated with *sulfamethylthiaz* (Berglund & Frisk) |
|---|---|---|---|---|
| Nausea, vomiting | 39 | 32 | 20 | ++ |
| Rash + fever .... | 8 | 1 | 9 | 1 |
| Hematuria ..... | 5 | 0 | 0 | 2 |
| Conjunctivitis .... | 2 | 0 | 2 | 0 |
| Neuritis..... | 0 | 0 | 3 | 4 |
| Hemotol. compl... | 0 | 0 | 0 | 0 |

few — except for the very important neurological complications which will be discussed later on.

Rash was in every instance accompanied by fever (»drug fever»). It occurred in 8 patients. The age of these patients, the day of treatment on which the rash appeared, and the total dose of sulfathiazol (ST) before its appearance were:

1) Age 21 months, on the 4' day of treatment, after 7½ g of ST.
2) » 30 years » » 4' » » » » 9 » » »
3) » 46 » » » 4' » » » » 17 » » »
4) » 49 » » » 10' » » » » 48 » » »
5) » 57 » . The rash appeared promptly on commencement of a second series of treatment, after 12 days' pause. Total dose in the first series: 25 g in 7 days. (Acquired medicamental allergy?)

6) Age 60 years. The rash appeared during the second series of treatment. In the first series the total dose was 34 g in 7 days, without any inconvenience. Pause of 6 days. In the second series, on the 4' day of treatment, after 12 g of ST, an extensive rash appeared together with slight fever. (Acquired medicamental allergy?)

7) Age 66 years, on the 4' day of treatment, after 16 g of ST.
8) » 72 » . The rash appeared during the second series of treatment, after 19 g of ST. Pause of 1 day. Total dose in the first series: 20 g in 5 days.

Table

*20 cases of Anterior +*

+ means that the respective abnormality was found in one or several of the

probably not

| Case No. | Record No. | Date(s) of attack(s) | No. of ECG. | Dates of electro-cardiograms. | Date of Death. |
|---|---|---|---|---|---|
| 22 | 830/39 | June 39? | 2 | 8/10—19/10 39 | 2/11 39 |
| 23 | 597/38 | Jan. 37—May 38? | 11 | 15/7—6/8 38 | 7/8 38 |
| 24 | 948/38 | Oct. 38—7/11 38 | 13 | 7/11—8/12 38 | 9.12 38 |
| 25 | 1019/38 | 1932—5/12 38 | 13 | 1933, 13/12—27/12 38 | 28/12 38 |
| 26 | 39/40 | ? | 5 | 12/1—17/1 40 | 17/6 40 |
| 27 | 831/36 | 19/10 36 | 1 | 19/10 36 | 20/10 36 |
| 28 | 305/41 | 1938—March 41? | 34 | 8/2—9/4 41 | 16 4 41 |
| 29 | 541/37 | 1932—Dec. 36 | 6 | 12/6—23/6 37 | 27/6 37 |
| 30 | 65/41 | ? | 1 | 22/1 41 | 24/1 41 |
| 31 | 367/41 | 23/4 41? | 2 | 26/4—28/4 41 | 3 5 41 |
| 32 | 596/40 | ? | 1 | 10/8 40 | 12.8 40 |
| 33 | 806/39 | ? | 4 | 9/10—24/10 39 | 25/10 39 |
| 34 | 722/37 | Nov. 34—Aug. 37 | 8 | 27/8—1/10 37 | 7 10 37 |
| 35 | 851/40 | ? | 1 | 19/11 40 | 27/11 40 |
| 36 | 502/37 | Febr. 36-Febr. 37? | 2 | 7/6—9/6 37 | 12/6 37 |
| 37 | 588/38 | 31/7—38 | 3 | 2/8 38 | 2.8 38 |
| 38 | 112/41 | ? | 5 | 1939, 8/2 41 | 9.2 41 |
| 39 | 500/41 | ca. 10/6 41 | 10 | 22/2—3/4 40, 24/6—26/6 41 | 26.6 41 |
| 40 | 310/40 | ? | 0 | — | 12 4 40 |
| 41 | 810/38 | ? | 0 | — | 24.10 38 |

*Hematuria* was observed in 5 cases. In every instance it was microscopic only and of brief duration:

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1) | Age | 11 | years, | on | the | 6' | day, | after | 12 g, | demonstr. only chemically |
| 2) | » | 28 | » | » | » | 4' | » | » | 17 » | » chemically and microscopically |
| 3) | » | 30 | » | » | » | 6' | » | » | 25 » | » only chem. |
| 4) | » | 68 | » | » | » | 5' | » | » | 20 » | » chem and microsc. |
| 5) | » | 85 | » | » | » | 3' | » | » | 14 » | » » » » |

It seems rather likely that we have been able to avoid the occurrence of macroscopic hematuria and anuria reported by other authors by the microscopic or chemical demonstration of hematuria in the daily routine of the examination for blood and immediate discontinuance of the treatment at the least sign of blood in the urine.

Rash occurred mostly in elderly patients, and it always presented the same features: Maculopapular elements from pea to cherry size in circumference resembling erythema nodosum, often interspersed with scanty, slightly itching, urticarial elements, localized chiefly to the extremities. In two cases the rash was acompanied by pronounced conjunctivitis, oedema of the face and slight joint complaints. The rash subsided completely, simultaneously with the fall in temperature, in 1—3 days — that is, far more rapidly than the specific erythema nodosum.

In two patients the first series of sulfathiazol treatment had induced a state of idiosyncrasy that was revealed by the prompt appearance of rash and fever at the commencement of the second series. Probably some of the other patients, too, who had a medicamental rash and fever, will prove hypersensitive on future administration of sulfathiazol. This possibility, which undoubtedly applies to the sulfanilamide derivatives in general, is always to be kept in mind on renewed treatment with sulfanilamide in patients who have previously received the same remedy, especially as drug fever, with or without any rash, may be accompanied by such a serious complication as agranulocytosis (Hegglin, Plum & Thomsen, Oldberg, Long & Bliss). In 3 of our cases with drug fever and rash the blood picture was watched carefully; there was no granulocytopenia.

## Discussion.

From our previous paper, published about 6 months ago, it is evident that the clinical experiences concerning the *sulfamethylthiazol* therapy at that time were very slight. Since then, several reports have been published which all emphasize that sulfamethylthiazol is just as effective as sulfapyridine, and that the action of sulfamethylthiazol is the same as sulfathiazol. Berglund & Frisk (Stockholm) have employed sulfamethylthiazol in 100 cases of various infectious diseases, including 64 cases of pneumonia in which this remedy was given alternatingly with sulfathiazol, with good result. In 4 cases, however, the employment of sulfamethylthiazol was associated with the appearance of neuritis — with refractory disabling pareses in 2 of these cases — and for this reason the sulfamethylthiazol therapy was given up.

Pool & Cook had favorable results from employment of sulfamethylthiazol in 35 patients with infections of the urinary passages, and they observed but few toxic symptoms, no neuritis. Hamburger & Ruegsegger, Brown & Herrell obtained excellent results in the treatment of pneumonia and staphylococcus aureus sepsis with sulfamethylthiazol; the former authors observed neuritis and paresis in 2 out of 8 cases treated; the latter observed neuritis in 3 out of 101 patients treated with this remedy. Telegdi treated epidemic meningitis with sulfamethylthiazol, with excellent results. Among 45 patients he noticed in 4 cases an early appearing transitory paresis of cranial nerves, but the connection of this phenomenon with the treatment seems very doubtful. Further, sulfamethylthiazol is said to have been employed in 500 additional cases reported in the following medical literature, but most of this is inaccessible to us at present.

In this country Eldahl has stated in a preliminary report that he has employed sulfamethylthiazol (Staphylamid »Leo») in 800 cases of pneumonia and other infectious diseases with good effect. Nothing particular is said about the toxic symptoms except that neuritis was observed in 4 patients, 2 of whom had paresis, and hematuria in a couple of cases. Further, O. Andersen has treated 20 children with Staphylamid, with excellent results, and found drug fever in one case, doubtful hematuria in one, and no instance

of neuritis. In 1941, furthermore, sulfamethylthiazol in the form of Staphylamid was employed a great deal by practitioners in the treatment of pneumonia, as far as we know, generally with good result, except in influenza pneumonia. Toxic symptoms, especially neurological, are mentioned but seldom.

*Sulfathiazol* has been tried out more extensively than sulfamethylthiazol. In particular, several careful investigations have been reported on the effect of toxicity of this drug as compared to sulfapyridine, especially by American authors (Scott & Jones; Gaisford & Whitelaw; Flippin, Schwartz & Rose; Violini, Lewitt & O'Neill; Spink & Hansen; Pepper & Ham; Callomon & Goodpastor; Long & Haviland; Plummer & collaborators). These authors found the effect of sulfathiazol to be identical with that of sulfapyridine though less dramatic — as was noticed also in our sulfamethylthiazol material. The case mortality in the materials of the above-mentioned authors was 10—15 %. In this country Friederichsen & Soelbye have reported on sulfathiazol treatment of 129 children with pneumonia, among whom the case mortality was only 1.5 %.

*Toxic Symptoms in Sulfathiazol Therapy.* — As is well known, the immediate gastro-intestinal symptoms are much milder than in sulfapyridine therapy. Other symptoms — hematuria, anuria, drug fever, rash, granulo-cytopenia, hemolytic anemia — have been observed in sulfathiazol therapy as well as in sulfapyridine therapy. But as yet is not plainly evident from the reports whether these symptoms are less frequent under sulfathiazol treatment. It appears, however, as if exanthema and drug fever are much more frequent under sulfathiazol treatment than in sulfapyridine therapy.

Exanthema and drug fever are stated to occur in 5—10 % of the treated cases, hematuria (chiefly microscopic) in 2—6 %. Anuria and agranulocytosis appeared to be extremely rare. On the whole, the frequency of toxic complications increases with the dose and the concentration of the drug in the blood, but they may appear also after low dose. Drug fever has been observed a few times after intake of the first dose in cases where the patient had been given the remedy previously. Allergic complications are the most frequent, though fortunately, not before the 4' day of treatment. The drug fever must not be mistaken for the rather frequent secondary rise

in temperature appearing within the first 12—48 hours after the institution of treatment, probably most often when the dosage is too low.

With exception of Berglund and Frisk, practically no authors have dealt with a comparative estimation of the toxic symptoms in sulfathiazol and sulfamethylthiazol therapy. Only the most serious symptoms, the neurological, are now beginning to stand out in fairly distinct outline. The seriousness and disabling tendency of these complications entitle them to a more thorough discussion.

Long; Long and collaborators and Barlow & Homburger found in animal experiments that the introduction of methyl or phenyl groups in the sulfathiazol molecule increased the toxicity of the drug. In a comprehensive experimental work on chicken, Bieter and collaborators (1941) have shown that all sulfanilamides produce organic changes in the peripheral nerves as well as in the spinal cord. They further found that the degree of the changes increased in intensity with the introduction of methyl and phenyl groups in the sulfanilamide molecule, so that the sulfanilamides could be set up after the degree of the injurious by-effects in the following succession: 1) sulfanilamide, 2) sulfapyridine, 3) sulfathiazol, 4) sulfamethylthiazol, 5) sulfanilyl-dimethyl-sulfanilamide (uliron) and 6) sulfaphenylthiazol. Accumulation of the drugs in the large nerve trunks could be demonstrated. The authors emphasize that their experimental results are not directly applicable to man, as chickens appear far more hypersensitive than higher species. Still, there appears to be a striking parallelism between the results obtained by the abovementioned authors in experiments on mice and chickens and the clinical observations now available on the tendency of these drugs to produce neuritis. In Table 5 we have recorded all the cases of unquestionable neuritis from employment of these drugs that we have been able to gather on going through the literature.

Of the sulfanilamide preparations, sulfanilamide and sulfapyridine have been employed the longest and hence in far more cases than sulfathiazol and sulfamethylthiazol. The tendency towards an increase in frequency of neuritis in methyl-substituted preparations is distinctly evident from Table 5. But, besides the $CH_3$ group, these drugs must contain other toxic factors, as the molecules of the sulfanilamides — apart from sulfathiazol and sulfamethylthiazol — are built up differently, and preparations without any methyl

**Table 5.**

*Severe Neurological Complications in Sulfanilamide Therapy.*

| | $CH_3$ groups | No. of patients treated | No. of patients with neurritis reported in the literature |
|---|---|---|---|
| | | | cl. references |
| Sulfanilamide .... | 0 | Innumerable | 6 (1, 7, 9, 36, 25) |
| Sulfapyridine .... | 0 | Numerous | 2 (27, 35) |
| Sulfathiazol ..... | 0 | ca. 1500 ? | 4 (5, 6, 7a) |
| Sulfamethylthiazol | 1 | 1000—1500? | 26 (7a, 13, 15, 16a, 19, 32) |
| Uliron ..... | 2 | ? | Many (cf. Long & Bliss, p. 268) |

groups have given similar neurological complications as the methyl-substituted compounds.

The pathogenesis of sulfanilamide neuritis has not been cleared up yet. The few investigations into this question reported so far suggest that the elimination of the sulfanilamides, especially their acetylation, produces disturbances in the intermediate metabolism of vitamin B (aneurin). Engelhardt and collaborators [1], working with pigeons, showed that the polyneuritis appearing after administration of diseptal B and uliron could be prevented and cured by administration of large doses of vitamin $B_1$ (Betaxin). In his monograph »Die Funktionen der Vitamine des B-Komplexes im Organismus» [2] (*l. c.*, p. 62) Jung discusses the results obtained by Engelhardt *et al.*, and on the basis of his own experimental findings and considerations, he arrives at the hypothesis that the aneurin in the form of acetylaneurin pyrophosphate has a detoxicating effect on the sulfanilamides by acetylation with its own acetyl group: »By inundation of the organism with sulfonamide the normal metabolism of vitamin B would thus be damaged to such an extent as to give rise to a vitamin $B_1$ deficiency resulting in neuritis.

Clinically the neurological symptoms induced by the various preparations showed largely the same picture: symptoms of peripheral neuritis with paresthesias, weakness of the peripheral musculature of the extremities, especially the lower, increasing to loss

[1] Klin. Wchnschr. 1938, p. 1325 and 1939, I, p. 774. Deutsche med. Wchnschr. 1938, p. 114 and 1213.

[2] Beihefte zur Zeitschr. f. Vitaminforschung, No. 1, 1940.

of motor functions, peroneal paresis, uni- or bilateral foot-drop, less frequently bilateral weakness of the musculature of the thumb, impairment of the optic nerve (1 case) and of the acoustic nerve (1 case). Both after sulfamethylthiazol and, especially, after uliron the paresess have been refractory and disabling. In one case that terminated fatally, after uliron, changes were found in the *spinal cord* (see *Long* & Bliss). The appearance of neuritis seems capricious but probably more frequent with high dosage of the remedy and, especially, protracted treatment — as emphasized by Hamburger & Ruegsegger, who employed very large doses in cases of sepsis.

One of the patients reported by Bieter & collaborators, who acquired acoustic and peroneal pareses, had received about 600 g of sulfathiazol in 5 ½ months. Brown & Herrell's 3 patients with pareses after sulfamethylthiazol had received respectively 79 g in about 1 ½ months, 38 g in 7 days, and 71 g in 13 days. A particularly inconvenient circumstance is the fact that the neuritis may make its appearance up to several weeks after the discontinuance of the treatment (Brown & Herrell).

It is not to be denied that these neurological complications have discouraged the employment of sulfamethylthiazol. In the Mayo Clinic, according to Brown & Herrell, the use of methylthiazol has now been given inf.; and in a report by the Council on Pharmacology and Chemistry of the American Medical Association it says that owing to the implied risk of neuritis this remedy cannot be recommended for clinical use. Also Berglund & Frisk who were particularly unfortunate in having 4 instances of neuritis among their 61 treated patients advise against the employment of sulfamethylthiazol.

We have been so fortunate not to meet with any instance of neuritis among our 75 sulfamethylthiazol-treated patients, in spite of a relatively high though brief dosage. This, we think, is more likely to be attributable to incidental good luck than to the preparation itself, as both American, Swedish and Danish preparations have been able to cause neurological complications.

We found the effects of sulfamethylthiazol and sulfathiazol to be alike. The same has been stated, indeed, by Berglund & Frisk, Brown & Herrell and Hamburger & Ruegsegger. No positive clinical observation as to a greater effectivity of sulfamethylthiazol — in particular, against staphylococcal infections — has been reported in

the literature. *In choosing between sulfathiazol and sulfamethylthiazol, then, we have to realize that the risk of inducing a neurologic complication in the patient undoubtedly is greater with employment of sulfamethylthiazol than with sulfathiazol.*

The introduction of the thiazol preparations have made the treatment of pneumonia much easier to carry through. Owing to their toxicity, however, these remedies too are not ideal. It is to be hoped, inded that less toxic sulfanilamide preparations will be put forth in a near future.

## 2. Sulfathiazol in Blood and Urine.

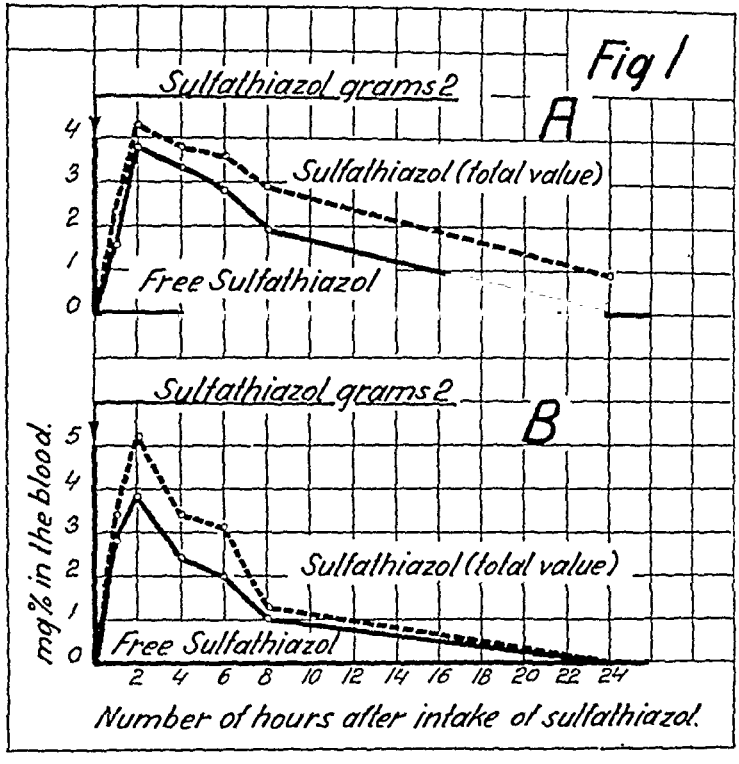
On 44 of the patients mentioned under section 1 the sulfathiazol concentration of the blood was estimated daily. In 10 of these cases the daily output of sulfathiazol in the urine was foolowed too. Only one of these patients, No. 51, may possibly have been treated with some remedy of the sulfanilamide group before admission to the hospital. The absorptive aspects of this patient are of particular interest, however, and hence she has been included in the present material. The blood samples were taken regularly at 9 a. m., about 3 hours after the last dose of sulfathiazol.

In our previous paper we reported some studies on the sulfamethylthiazol concentration of the blood and urine in 25 pneumonic patients who were treated exclusively with this drug. The purpose of our present work will be to present our studies on the corresponding aspects for sulfathiazol and compare the results thus obtained with the same dosage and with employment of the same technique of examination. So the account of the two series is made up after the same principles.

For determination of the concentrations we used the Marshall method as modified by Frisk.

In our previous paper it was pointed out that in the analysis of the blood the protein precipitation is associated with a constant loss of 16—18 % of an added amount of sulfamethylthiazol and acetyl sulfamethylthiazol. Something similar was found in the plotting of »Eich» curves for sulfathiazol, the protein precipitation being constantly associated with a loss of 9—13 % of the free form of the substance as well as its acetyl compound. As to the details, of the analyses, the reader is referred to the mentioned paper.

In two afebrile adult patients with irrelevant disease the concentration of sulfathiazol in the blood and urine was examined after a single dose of 2 g. The outcome of these analyses is evident from Fig. 1 (curves A and B). From the curves it will be noticed that sulfathiazol in both cases reached its maximal concentration in the blood after two hours, and that 7—8 hours after the intake the




concentration had fallen off to about one-half. After 24 hours no sulfathiazol could be demonstrated in the blood. The degree of acetylation was about the same in the two cases; on an average 70—80 % of the drug was found as free sulfathiazol.

In the first 24 hours the urine was divided into 3 portions of 6, 6 and 12 hours' output. The total excretion in the first 24-hours amounted respectively to 54 % and 49 % of the intake. Of these excretions 71 % and 42 % appeared as free sulfathiazol. The first portion of urine contained respectively 28 % and 21 % of the excreted amount, the second portion 27 % and 14 %, and the third 45 % and 65 %. The urine excreted in the next 48 hours was examined as 24-hour urines. The excretion of sulfathiazol ceased

on the second day after the intake; the total excretion amounted to 63 % and 71 % of the ingested dose.

On comparison of these results with our previous findings concerning sulfamethylthiazol, the most essential difference is the lesser degree of acetylation of sulfathiazol in the blood as well as in the urine. The maximal total sulfathiazol concentration of the blood appears to be somewhat lower than that of sulfamethylthiazol, averaging 4.7 mg %; on administration of sulfamethylthiazol the average concentration was 6.1 mg %. Besides, the elimination of sulfathiazol proceeds somewhat more rapidly than that of sulfamethylthiazol. While sulfathiazol was eliminated from the blood completely in less than 24 hours, a demonstrable amount of sulfamethylthiazol was still present in the blood as long as 51 hours after the intake. Accordingly, it took longer before the excretion of the sulfamethylthiazol ceased, small amounts of the drug being present in the urine even on the third day after the intake. On the other hand, the total excretion of the two substances was approximately the same.

Our studies on sulfathiazol are largely in harmony with the findings reported previously for these discussions (Simesen; Gsell). That sulfathiazol disappears from the blood more rapidly than sulfamethylthiazol is in agreement with some previous studies on the renal clearance of various sulfanilamides, the clearance rate being highest for sulfathiazol (Strauss, Lowell, Taylor & Finland; Frisk). Another important factor in the elimination of the drug is its combustion in the organism. In a number of experiments it has been demonstrated that 40—50 % of a given amount of sulfathiazol is combusted within 10—12 hours (Simesen). As far as we have been able to find out, no similar studies have been carried out concerning sulfamethylthiazol.

Table 6 gives the daily intake of sulfathiazol, the concentration of free and total sulfathiazol in the blood, and — for 10 of the patients — the total excretion of sulfathiazol with the urine.

The concentration of free sulfathiazol in the blood rose rapidly in the first 12—36 hours of treatment; an additional rise that had to be taken into consideration was seen only in 4 cases Nos. 28, 33, 51 and 81). In 90 % of the cases the concentration of the drug in the blood reached its maximum within 60 hours of treatment. In one case only was a maximum concentration not reached till after 100

## Table 6.

*Daily Dose of Sulfathiazol; Free and Total Sulfathiazol in the Blood; and — for 10 of the Patients — the Total Excretion of Sulfathiazol with the Urine.*

The numbers of the patients correspond to the numbers in Table 1.

| Pt. No. | Day of treatment | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 | ST dose (in g) | 3 | 3 | 1 | | | | | | | | | | | Total intake: 7.0 g. |
| | ST in blood, free | 4.4 | 6.4 | 4.1 | 0.5 | 0.0 | | | | | | | | | Total excret.: 5.5 g = 78 % of intake. |
| | (mg %) total | 5.1 | 8.9 | 6.0 | 1.7 | 0.0 | | | | | | | | | Excretion of free ST: 4.8 g = 87 % of total excretion. |
| 28 | ST dose (in g) | 3 | 3 | 2 ½ | 2 ½ | 2 ½ | 2 ½ | 2 ½ | ½ | | | | | | Total intake: 19 g |
| | ST in blood, free | | 1.8 | 0.8 | 4.4 | 3.8 | 2.6 | 2.7 | 4.8 | 4.0 | 0.0 | | | | |
| | (mg %) total | | 3.4 | 1.6 | 5.8 | 5.1 | 3.8 | 3.5 | 6.8 | 5.5 | 0.9 | | | | |
| 31 | ST dose (in g) | 2 ½ | 3 | 3 | 3 | 3 | | | | | | | | | Total intake: 14 ½ g |
| | ST in blood, free | | 3.5 | 3.6 | 3.6 | 3.6 | 3.7 | 0.0 | | | | | | | |
| | (mg %) total | | 4.3 | 3.8 | 5.1 | 5.0 | 4.6 | 0.0 | | | | | | | |
| 32 | ST dose (in g) | 3 | 3 | 3 | 2 | | | | | | | | | | Total intake: 11 g |
| | ST in blood, free | | 2.4 | 3.7 | 3.3 | 0.8 | 0.0 | | | | | | | | |
| | (mg %) total | | 3.8 | 5.4 | 4.3 | 1.3 | 0.0 | | | | | | | | |
| 33 | ST (dose (in g) | 5 | 6 | 5 | 5 | 1 | | | | | | | | | Total intake: 22 g |
| | ST in blood, free | | 1.3 | 2.7 | 6.1 | 4.9 | 0.0 | | | | | | | | |
| | (mg %) total | | 2.2 | 4.8 | 7.1 | 6.3 | 0.6 | | | | | | | | |
| 34 | ST dose (in g) | 2 ½ | 3 | 3 | 3 | ½ | | | | | | | | | Total intake: 12 g. |
| | ST in blood, free | | 2.8 | 4.7 | 2.1 | 1.9 | 1.5 | 0.0 | | | | | | | |
| | (mg %) total | | 3.6 | 5.6 | 3.1 | 2.9 | 2.4 | 0.6 | | | | | | | |
| 35 | ST dose (in g) | 3 ¾ | 4 ½ | 4 ½ | 2 | 2 | 4 | 4 | 4 | 1 | | | | | Total intake: 29 ¾ g. |
| | ST in blood, free | | 3.8 | 5.6 | 6.3 | 0.6 | 0.7 | 3.2 | 1.5 | 3.4 | 1.6 | 0.0 | 0.0 | | |
| | (mg %) total | | 4.5 | 6.5 | 7.4 | 1.1 | 1.4 | 4.4 | 2.8 | 4.5 | 3.0 | 1.1 | 0.0 | | |
| 36 | ST dose (in g) | 4 | 6 | 6 | 6 | 6 | 4 | 1 | | | | | | | Total intake: 33 g. |
| | ST in blood, free | | 5.9 | 6.7 | 7.0 | 6.2 | 5.2 | 1.1 | 1.8 | 0.0 | | | | | |
| | (mg %) total | | 7.4 | 8.6 | 9.8 | 7.3 | 8.0 | 2.9 | 2.1 | 0.0 | | | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37 | ST dose (in g) | 5 | 5 | 5 | 5 | 1 | | | | | | | | | Total intake: 21 g. |
| | ST in blood, free (mg %) | | 3.9 | 4.5 | 5.0 | 3.8 | | | | | | | | | |
| | total | | 5.7 | 6.0 | 6.2 | 4.7 | | | | | | | | | |
| 39 | ST dose (in g) | 5 | 6 | 6 | 6 | 4 | 1 | | | | | | | | Total intake: 28 g. |
| | ST in blood, free (mg %) | | | 3.8 | 4.0 | 5.1 | 0.8 | 0.0 | | | | | | | |
| | total | | | 4.8 | 5.3 | 6.9 | 1.7 | 0.0 | | | | | | | |
| 40 | ST dose (in g) | 5 | 6 | 6 | 5 | 5 | | | | | | | | | Total intake: 27 g. |
| | ST in blood, free (mg %) | | 4.2 | 4.1 | 3.8 | 3.9 | | | | | | | | | |
| | total | | 6.6 | 6.7 | 5.3 | 5.8 | | | | | | | | | |
| 41 | ST dose (in g) | 5 | 6 | 6 | 6 | | | | | | | | | | Total intake: 23 g. Total excret.: 10.1 g = 44 % cf intake. Excretion of free ST: 8.7 g = 85 % of total excretion. |
| | ST in blood, free (mg %) | | 5.9 | 5.5 | 4.6 | 5.2 | 0.0 | 0.0 | | | | | | | |
| | total | | 7.1 | 6.3 | 5.3 | 6.0 | 1.2 | 0.0 | | | | | | | |
| 45 | ST dose (in g) | 5 | 6 | 6 | 6 | 6 | 4 | | | | | | | | Total intake: 33 g. |
| | ST in blood, free (mg %) | | 3.0 | 5.4 | 6.3 | 5.7 | 4.9 | 1.2 | 0.0 | | | | | | |
| | total | | 4.0 | 6.3 | 7.7 | 6.8 | 5.9 | 3.2 | 1.2 | | | | | | |
| 48 | ST dose (in g) | 4 | 6 | 6 | 6 | 6 | | | | | | | | | Total intake: 28 g. Total excret.: 12.6 g = 45 % cf intake. Excretion offree ST: 9.7 g. = 77 % of total excretion. |
| | ST in blood, free (mg %) | | 6.0 | 4.2 | 3.9 | 4.0 | 3.1 | 0.0 | | | | | | | |
| | total | | 7.2 | 5.3 | 7.2 | 5.0 | 4.8 | 0.2 | | | | | | | |
| 50 | ST dose (in g) | 4 | 6 | 5 | 6 | 2 | | | | | | | | | Total intake: 28 g. |
| | ST in blood, free (mg %) | | 4.1 | 5.8 | 6.1 | 5.0 | 4.3 | 0.0 | | | | | | | |
| | total | | 4.9 | 6.5 | 6.9 | 5.9 | 5.6 | 0.0 | | | | | | | |
| 51 | ST dose (in g) | 6 | 7 | 6 | 6 | 6 | 6 | 0 | 5 | 6 | 1 | | | | Total intake: 51 g. |
| | ST in blood, free (mg %) | | 0.2 | 2.1 | 14.2 | 9.6 | 4.2 | 3.2 | 0.0 | 3.5 | 5.1 | 0.0 | | | |
| | total | | 0.3 | 3.2 | 17.6 | 10.9 | 5.8 | 4.3 | 0.0 | 5.0 | 6.6 | 0.0 | | | |
| 52 | ST dose (in g) | 5 | 6 | 6 | 4 | 4 | 1 | | | | | | | | Total intake: 26 g. Total excret.: 11.4 g = 44 % of intake. Excretion of free ST: 8.8 g = 74 % of total excretion. |
| | ST in blood, free (mg %) | | 4.8 | 3.7 | 2.6 | | 2.2 | | 0.0 | | | | | | |
| | total | | 6.6 | 5.2 | 4.1 | | 3.4 | | 0.0 | | | | | | |

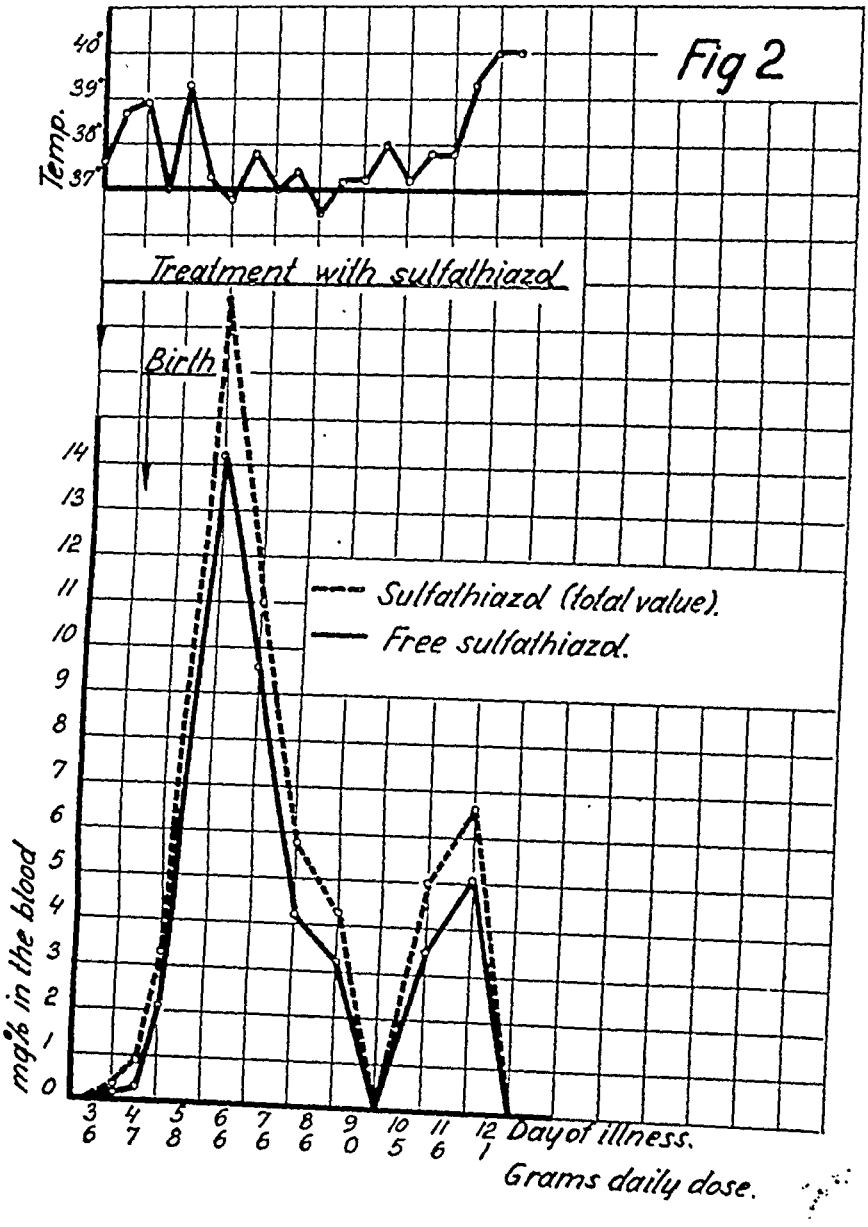
**Table 6.** (Cont. 1.)

| Pt. No. | Day of treatment | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 53 | ST dose (in g) | 2 | 7 | 4 | | | | | | | | | | | Total intake: 13 g. |
| | ST in blood, free | | 1.1 | 4.0 | 0.3 | 0.0 | | | | | | | | | |
| | (mg %) total | | 2.4 | 5.6 | 1.3 | 0.0 | | | | | | | | | |
| 57 | ST dose (in g) | 6 | 6 | 6 | 6 | 6 | 6 | 2 | | | | | | | Total intake: 32 g. |
| | ST in blood, free | | 6.1 | 2.1 | 7.4 | 3.6 | 5.5 | 3.9 | 0.0 | 0.0 | | | | | |
| | (mg %) total | | 7.2 | 3.4 | 9.0 | 4.8 | 7.5 | 5.6 | 1.5 | 0.0 | | | | | |
| 59 | ST dose (in g) | 4 | 6 | 6 | 6 | 6 | 6 | 6 | 1 | | | | | | Total intake: 41 g. |
| | ST in blood, free | | 1.1 | 8.1 | 3.4 | 3.6 | 3.0 | 3.6 | 2.6 | 0.0 | 0.0 | | | | Total excret.: 20.9 g = 51 % of intake. |
| | (mg %) total | | 1.8 | 9.0 | 4.3 | 5.0 | 4.3 | 4.7 | 3.1 | 0.4 | 0.0 | | | | Excretion of free ST: 17.0 g = 80 % of total excretion. |
| 60 | ST dose (in g) | 7 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 1 | | | | | Total intake: 50 g. |
| | ST in blood, free | | 2.3 | 8.3 | 7.0 | 9.0 | 6.5 | 7.7 | 3.8 | 3.1 | 3.8 | 0.0 | | | Total excret.: 35.9 g = 72 % of intake. |
| | (mg %) total | | 3.1 | 10.0 | 8.5 | 15.6 | 7.3 | 8.8 | 5.2 | 4.2 | 4.8 | 0.4 | | | Excretion of free ST: 30.2 g = 84 % of total excretion. |
| | ST dose (in g) | 6 | 6 | 6 | 2 | | | | | | | | | | Total intake: 20 g. |
| | ST in blood, free | | 6.8 | 7.5 | 6.1 | 2.0 | 0.0 | | | | | | | | |
| | (mg %) total | | 7.7 | 8.6 | 7.3 | 3.0 | 0.0 | | | | | | | | |
| 61 | ST dose (in g) | 6 | 6 | 6 | 6 | 5 | 6 | 6 | 1 | | | | | | Total intake: 42 g. |
| | ST in blood, free | | 5.0 | 5.8 | 2.0 | 3.4 | 6.5 | 3.6 | 3.7 | 0.0 | | | | | Total excret.: 30.1 g = 72 % of intake. |
| | (mg %) total | | 6.0 | 7.5 | 3.1 | 4.8 | 7.9 | 4.2 | 5.3 | 0.7 | | | | | Excretion of free ST. 23.7 g = 79 % of total excretion. |
| 62 | ST dose (in g) | 4 | 8 | 6 | 6 | | | | | | | | | | Total intake: 24 g. |
| | ST in blood, free | | 4.4 | 7.7 | 5.2 | 3.0 | | | | | | | | | |
| | (mg %) total | | 5.8 | 8.8 | 6.9 | 4.0 | | | | | | | | | |
| 63 | ST dose (in g) | 6 | 6 | 6 | 6 | 6 | 4 | 4 | 5 | 6 | 6 | | | | Total intake: 55 g. |
| | ST in blood, free | | 3.4 | 7.0 | 5.1 | 7.1 | 3.9 | 7.7 | 1.2 | 3.3 | 4.6 | 5.0 | 0.0 | 0.0 | |
| | (mg %) total | | 5.1 | 8.2 | 6.3 | 8.2 | 4.5 | 8.9 | 2.1 | 5.6 | 6.0 | 5.9 | 0.9 | 0.0 | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 67 | ST dose (in g) | 5 | 6 | 6 | 6 | 6 | 4 | 4 | 4 | 4 | | | | | Total intake: 45 g. |
| | ST in blood, free | | 3.1 | 4.4 | 2.5 | 2.1 | 3.9 | 1.0 | 0.8 | 1.2 | 0.0 | 0.0 | | | Total excret.: 29.4 g = 65 % of intake. |
| | (mg %) total | | 5.2 | 6.4 | 4.7 | 3.4 | 5.2 | 3.3 | 1.8 | 2.1 | 1.8 | 0.5 | | | Excretion of free ST: 20.3 g = 69 % of total excretion. |
| 69 | ST dose (in g) | 3 | 6 | 6 | 6 | 6 | 6 | 4 | 4 | 1 | | | | | Total intake: 42 g. |
| | ST in blood, free | | 3.1 | 5.4 | 4.4 | 4.0 | 4.9 | 4.6 | 0.4 | 2.0 | 0.4 | 0.0 | | | |
| | (mg %) total | | 5.5 | 6.7 | 5.9 | 6.4 | 6.4 | 7.8 | 2.1 | 3.2 | 1.2 | 0.0 | | | |
| 70 | ST dose (in g) | 4 | 6 | 6 | 6 | 4 | 4 | 4 | | | | | | | Total intake: 34 g. |
| | ST in blood, free | | 5.8 | 6.4 | 6.7 | 5.5 | 1.9 | 2.1 | 1.1 | 6.3 | 0.0 | | | | |
| | (mg %) total | | 7.9 | 8.5 | 8.8 | 6.9 | 5.2 | 3.7 | 1.7 | 7.4 | 0.5 | | | | |
| 71 | ST dose (in g) | 5 | 6 | 6 | 4 | 1 | | | | | | | | | Total intake: 22 g. |
| | ST in blood, free | | 5.2 | 5.3 | 4.4 | 3.5 | 0.7 | 1.0 | 0.0 | | | | | | |
| | (mg %) total | | 6.6 | 7.8 | 6.9 | 4.8 | 1.6 | 2.3 | 0.0 | | | | | | |
| 72 | ST dose (in g) | 5 | 6 | 6 | 6 | | | | | | | | | | Total intake: 23 g. |
| | ST in blood, free | | 7.1 | 6.3 | 7.4 | | | | | | | | | | |
| | (mg %) total | | 8.5 | 8.6 | 11.2 | | | | | | | | | | |
| 74 | ST dose (in g) | 6 | 6 | 6 | 4 | 6 | | | | | | | | | Total intake: 28 g. |
| | ST in blood, free | | 6.4 | 6.6 | | 2.2 | 7.2 | | | | | | | | |
| | (mg %) total | | 7.8 | 7.7 | | 3.0 | 8.4 | | | | | | | | |
| 75 | ST dose (in g) | 4 | 6 | 6 | 6 | 1 | | | | | | | | | Total intake: 23 g. |
| | ST in blood, free | | 4.5 | 3.2 | 4.3 | | | 0.0 | 0.0 | | | | | | Total excret.: 11.9 g = 52 % of intake. |
| | (mg %) total | | 5.6 | 4.1 | 5.2 | | | 0.8 | 0.0 | | | | | | Excretion of free ST: 9.8 g = 80 % of total excretion. |
| 77 | ST dose (in g) | 3 | 6 | 6 | 6 | 5 | 1 | | | | | | | | Total intake: 27 g. |
| | ST in blood, free | | 5.0 | 4.9 | 5.3 | 4.2 | 3.2 | 2.7 | 0.0 | | | | | | |
| | (mg %) total | | 7.0 | 6.3 | 7.2 | 5.9 | 5.0 | 3.5 | 0.0 | | | | | | |
| 78 | ST dose (in g) | 6 | 6 | 6 | 6 | 4 | 4 | 4 | | | | | | | Total intake: 36 g. |
| | ST in blood, free | | 5.2 | 4.3 | 5.8 | 4.2 | 1.4 | 0.5 | 2.1 | 0.0 | | | | | |
| | (mg %) total | | 6.4 | 5.3 | 6.7 | 5.3 | 2.4 | 1.7 | 3.2 | 1.9 | | | | | |

Table 6. (Cont. 2.)

| Pt. No. | Day of treatment | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 79 | ST dose (in g) | 5 | 6 | 6 | 6 | 2 | | | | | | | | | Total intake: 25 g. |
| | ST in blood, free | | | 7.2 | 8.3 | 7.2 | 1.5 | 0.0 | | | | | | | |
| | (mg %) total | | | 10.0 | 10.0 | 9.9 | 3.5 | 1.0 | | | | | | | |
| 80 | ST dose (in g) | 4 | 6 | 6 | 6 | 6 | 6 | | | | | | | | Total intake: 34 g. |
| | ST in blood, free | | 5.7 | 4.4 | 5.3 | 4.0 | 5.2 | 0.0 | | | | | | | |
| | (mg %) total | | 7.2 | 5.2 | 6.3 | 5.1 | 6.1 | 0.5 | | | | | | | |
| 81 | ST dose (in g) | 6 | 4 | 6 | 6 | 4 | 2 | | | | | | | | Total intake: 28 g. |
| | ST in blood, free | | 7.8 | 6.4 | 9.8 | 11.7 | 6.0 | 1.4 | | | | | | | |
| | (mg %) total | | 9.6 | 7.9 | 12.4 | 13.7 | 12.5 | 3.2 | | | | | | | |
| 82 | ST dose (in g) | 4 | 4 | 4 | 4 | 1 | | | | | | | | | Total intake: 17 g. |
| | ST in blood, free | | 4.9 | 1.9 | 2.7 | 6.4 | 0.0 | | | | | | | | |
| | (mg %) total | | 5.7 | 2.3 | 3.3 | 7.3 | 0.7 | | | | | | | | |
| 83 | ST dose (in g) | 4 | 6 | 6 | 6 | 6 | 1 | | | | | | | | Total intake: 29 g. |
| | ST in blood, free | | 4.4 | 7.2 | 5.7 | 7.5 | 4.4 | 1.5 | 0.0 | | | | | | Total excret.: 15.5 g = 53 % of intake. |
| | (mg %) total | | 5.3 | 8.5 | 7.3 | 9.3 | 6.3 | 2.7 | 0.0 | | | | | | Excretion of free ST: 11 g = 71 % of total excretion. |
| 85 | ST dose (in g) | 4 | 6 | 6 | 3 | 1 | | | | | | | | | Total intake: 20 g. |
| | ST in blood, free | | 4.5 | | 1.2 | 0.4 | | | | | | | | | |
| | (mg %) total | | 6.7 | | 3.0 | 1.7 | | | | | | | | | |
| 88 | ST dose (in g) | 5 | 6 | 4 | 4 | 2 | | | | | | | | | Total intake: 21 g. |
| | ST in blood, free | | 8.6 | 11.3 | 6.2 | 4.2 | 0.9 | 0.0 | | | | | | | |
| | (mg %) total | | 10.0 | 12.4 | 7.3 | 5.0 | 1.5 | 0.0 | | | | | | | |
| 90 | ST dose (in g) | 1 | 4 | 4 | 4 | 4 | 4 | | | | | | | | Total intake: 21 g. |
| | ST in blood, free | | 1.9 | 3.9 | 1.8 | 0.8 | 2.4 | 2.4 | 0.0 | | | | | | |
| | (mg %) total | | 3.3 | 5.9 | 3.2 | 2.1 | 3.7 | 3.7 | 0.5 | | | | | | |




hours of treatment. Notwithstanding a uniform and constant dosage, in the following days the concentrations often showed a certain tendency to fall off.

As mentioned before, the absorptive conditions in patient No. 51 showed some interesting features (Fig. 2).

This patient was a woman, 30 years old, in the 8' month of pregnancy in whom the lobar pneumonia involved the entire right lung and the inferior lobe of the left lung. She was given sulfathiazol (»large cure»).

In the first 24 hours of treatment the sulfathiazol concentration of the blood rose but very slowly, although she was treated after the usual principles. Labor set in 21 hours after the institution of treatment. The sulfathiazol concentration of the blood was minimal — 3 hours before and 4 hours after the parturition. The 24-hour dose was increased, and in the next 36 hours the concentration of free sulfathiazol rose to about 14 mg %. On the 9' day of illness the treatment was discontinued, but it was resumed again as early as on the next day. This time the sulfathiazol concentration of the blood did not deviate from the average obtained for the rest of this material. These findings might suggest that the slow rise in the concentration in the beginning of the treatment was due to a slow absorption of the drug from the intestinal canal on account of the pregnancy of the patient, as an abnormal blood distribution or stasis in the abdominal organs resulting from the gestation might conceivably delay the absorption of the drug.

In order to throw some light on this question, we examined the sulfathiazol concentration of the blood in 3 normal parturient women in the Lying-in Department A of the Rigshospital [1] — 3 hours after a single peroral dose of 2 g of sulfathiazol. The obtained results are recorded in Table 7.

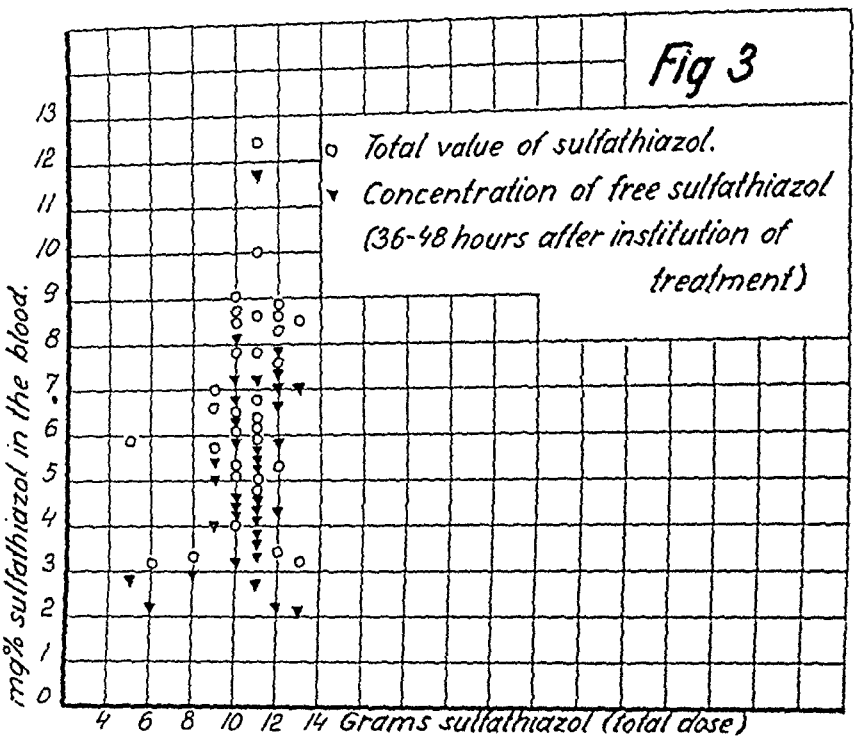
**Table 7.**

*Sulfathiazol Concentration of the Blood in 3 Normal Parturient Women 3 Hours after Peroral Intake of 2 g. Sulfathiazol.*

| Patient No. | 1 | 2 | 3 |
|---|---|---|---|
| Concentration of free sulfathiazol in the blood in mg % | 2.8 | 3.4 | 2.5 |
| Concentration of total sulfathiazol in the blood in mg % | 3.5 | 4.1 | 2.8 |

On comparison of these findings with the tolerance curves A and B in Fig. 1, there is no demonstrable delay in the absorption of sulfathiazol from the intestinal canal in normal parturient women. So the slow rise in the sulfathiazol concentration of the blood in patient No. 51 must have been due to other conditions.

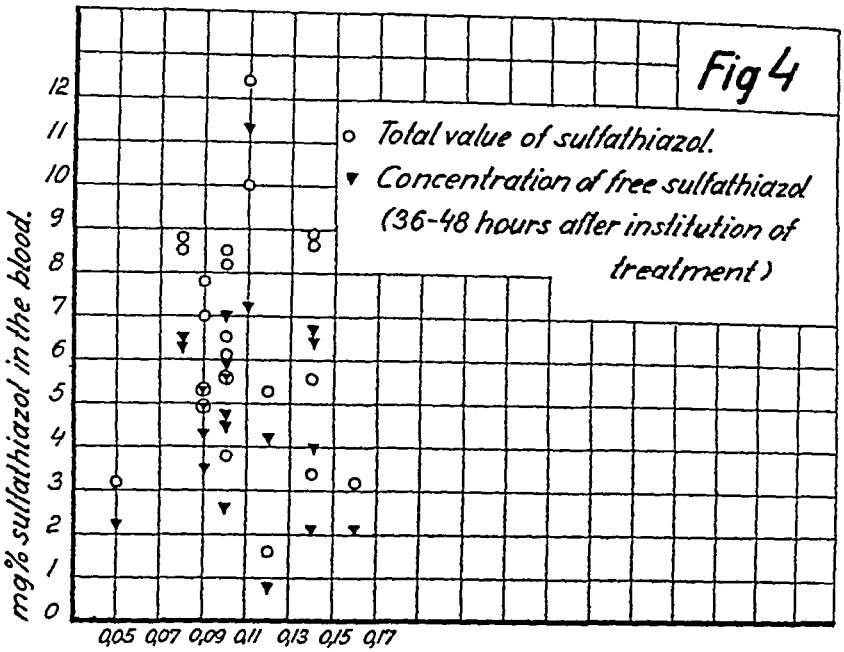
[1] We are greatly obliged to Professor E. Rydberg, M. D. for permission to carry out there studies in his department.




In Fig. 3 we have recorded all the concentrations of sulfathiazol, free as well as total, in the blood after treatment for 36—48 hours. From this it is evident that there is no constant relation between the size of the dose and the sulfathiazol concentration of the blood obtained in the various patients on peroral administration of the drug. The same holds true when the 24-hour dose is calculated in grams per kilogram of body weight (Fig. 4).

During the treatment the degree of acetylation in the blood showed only moderate variations and was distributed as follows: In 66 % of all the determinations the free sulfathiazol made up over 70 % of the total value, in 25 % it amounted to 50—70 %, and in the remaining cases it was most often 30—50 % of the total value.

Only in 6 cases (Nos. 28, 31, 59, 60, 62 and 65) did the treatment, in the first 36—48 hours, not give a critical fall in temperature to below 38° and maintenance of this level. In No. 28 the concentration of free sulfathiazol in the blood rose rather slowly and, correspondingly a lasting effect on the temperature did not appear till after treatment for about 60 hours; the concentration was then 4—5 mg %. In the remaining 5 patients, on the other




hand, the concentration of free sulfathiazol in the blood was on an average of the same magnitude as found in the patients in whom the temperature fell to a level below 38° within the first 36—48 hours of treatment. In 1 patient (No. 31) the temperature fell by lysis in 4 days, in 3 (Nos. 59, 60 and 62) complications developed and in 1 patient (No. 65) there was practically no effect from the treatment. Two of these patients died (Nos. 62 and 65).

In the 10 patients in whom the 24-hour output of the drug in the urine was followed, the total excretion was on an average 50 % of the total intake. The greatest excretion was found in patient No. 25, in whom 78 % was recovered. In all these cases the degree of acetylation was fairly constant; 70—80 % of the excreted amount was found as free sulfathiazol.

## Discussion.

The above-mentioned loss (9—13 %) of the drug by the protein precipitation in the blood analysis is in agreement with the findings reported by Sundermann & Pepper as far as free sulfathiazol is concerned, for which these authors found an average loss of 14 %,

whereas they found the loss of the acetyl compound was found to be 21 %. In contrast hereto, Frisk was able to recover the added amounts of sulfathiazol and acetyl sulfathiazol quantitatively when the analysis was carried out on blood.

*Our studies on sulfathiazol* showed briefly. Rapid rise in the sulfathiazol concentration of the blood in the first 12—36 hours of treatment; large individual variations in the concentrations obtained. No proportionality between the size of the doses and the blood concentrations obtained in the various patients; most often a rather slight degree of acetylation. About 50 % of the given amount was generally recovered in the urine, with 70—80 % of the excreted drug as free sulfathiazol.

Largely, these results agree with the findings recorded by Frisk, by Gsell and by Simesen. Still, with the same dosage we generally obtain higher concentrations in the blood than found by Frisk and by Simesen. The values obtained by us were more in harmony with those reported by Gsell — that is, when we take into consideration that Gsell's analyses were carried out on serum, in which the concentration is 1 ½ times higher than in whole blood (Simesen). Like our findings, with uniform dosage, the analyses reported by Gsell and by Simesen showed great individual variations in the blood concentrations; and this is in conflict with the results reported by Frisk. The total output in the urine was somewhat lower than reported by Simesen, and more in harmony with the findings of Gsell. The low degree of acetylation in the urine has been found by all investigators.

Frisk has stated that a sudden increase in the acetylsulfathiazol concentration of the blood often is a precursor of toxic symptoms. While our studies were going on, a medicamental rash developed in 4 cases (Nos. 53, 60, 63 and 79). In the days preceding this complication, in patient No. 63 there appeared a moderate rise in the acetylsulfathiazol concentration of the blood, while earlier in the treatment the concentration had kept fairly constant. In the remaining 3 patients no such change was seen in the acetylsulfathiazol content of the blood.

*On comparison of our results for sulfathiazol with our previously reported findings for sulfamethylthiazol* the most striking difference is the one in the percental amount of the two substances found in free form in the blood: with sulfamethylthiazol an even distribution

of the values from 20 % to 90 %, with sulfathiazol over 50 % in a greater majority of the cases. In contrast hereto, Becker-Christensen has recently found free sulfamethylthiazol to make up to 60—70 % of the total value of this substance in the blood.

Generally the acetylated compound is stated to be less toxic than the free substance (K. O. Møller). Still, Clark says that the acetylated compound is the more toxic.

For comparison of the obtained blood concentrations of sulfathiazol and sulfamethylthiazol on uniform dosage, in Table 8 we have recorded collectively the concentrations observed in a number of adult pneumonic patients who were treated respectively with a daily dose of 6 g of sulfathiazol and sulfamethylthiazol.

**Table 8.**

*Comparison between the Blood Concentrations of the Drugs obtained in a Number of Pneumonic Patients treated with Equally Large Doses of Sulfathiazol and Sulfamethylthiazol, respectively.*

| Mg. % of sulfanilamide in the blood | | 0—3 | 3—6 | 6—9 | >9 |
|---|---|---|---|---|---|
| Percental distribution of the *sulfathiazol* concentrations in a number of pneumonic patients (115 determinations) | Free | 7 | 64 | 25 | 4 |
| | Total | 1 | 41 | 47 | 11 |
| Percental distribution of the sulfamethylthiazol concentrations in a number of pneumonic patients (47 determinations) | Free | 34 | 26 | 17 | 23 |
| | Total | 0 | 36 | 19 | 45 |

From Table 8 it is evident that the variation of the obtained blood concentrations on uniform dosage was greater on employment of sulfamethylthiazol than with sulfathiazol. Only 43 % of all the sulfamethylthiazol values were from 3 to 9 mg %, whereas 89 % of the sulfathiazol values fell within these limits. Thus, values below 3 mg % and over 9 mg % were far more frequent under treatment with sulfamethylthiazol than with sulfathiazol.

Turning to the rate at which the two substances are eliminated from the blood, it is found to be higher for sulfathiazol as about 90 % of the patients had no free sulfathiazol in the blood 2 days after the discontinuance of this medication, while only 50 % of the sulfamethylthiazol-treated patients showed a corresponding eli-

mination. This harmonizes with the aforementioned studies on the renal clearance which is greater for sulfathiazol.

The total excretion of the 2 substances is found to make nearly the same percentage of the intake. With sulfamethylthiazol there appeared to be a certain relation between the size of the daily dose and the percental output of the substance with the urine, insofar as the output as a rule was decreasing with increasing dosage. As the daily doses given the sulfathiazol-treated patients were more uniform in the cases in which we examined the excretion with the urine, the possibility of such a relation could not be looked into here. On comparison of the degree of acetylation of the two substances in the urine, it is found to be greater for sulfamethylthiazol as about 50 % of the excreted drug was acetylated. For sulfathiazol the corresponding value was found to be 20—30 %.

*So, according to our chemical analyses, sulfathiazol differs from sulfamethylthiazol in the following respects:*

1) Less acetylation in the blood. (The chemotherapeutic effect of the acetyl compounds is taken to be very slight.

2) Less dispersion of the blood concentration obtained with a certain dosage.

3) More rapid excretion from the organism.

4) Less acetylation in the urine. [The acetylated compound is stated to be about 10 times less soluble than the free (Sundermann & Pepper).]

5) Sulfathiazol is stated to be 4—5 times more easily soluble than sulfamethylthiazol (Frisk).

Owing to the two last-mentioned qualities it will be reasonable a priori to presume that *hematuria* occurs more frequently under treatment with sulfamethylthiazol. Clinical experiences show, however, that the opposite is the case (Brown & Harrell; Buch, Engbæk & Nissen). This observation might conceivably be explained as due perhaps to the circumstance that the more rapid excretion of sulfathiazol from the organism may bring about a higher concentration of this substance in the urine and thus an increased tendency to crystallization.

## Summary.

1. Altogether 92 patients with lobar pneumonia were treated with sulfathiazol. The case mortality was 10.9 %. After deduction of 5 patients, over 60 years old, in whom the cause of death was cardiac disease, the case mortality may properly be corrected to 5.5 %. The corresponding death rate for a previously reported material of sulfamethylthiazol-treated patients was 8.0 %, corrected to 4.4 %, for 75 patients. So the effect of sulfathiazol is considered equal to that of sulfamethylthiazol.

2. A review is given of the toxic symptoms produced by sulfathiazol therapy. Compared to the group of sulfamethylthiazol-treated patients, the sulfathiazol group showed more cases of rash and, especially, hematuria; but all these cases were mild and inconveniencing but little.

3. In the discussion the literature is reviewed briefly with reference to complications ascribable to sulfathiazol and sulfamethylthiazol, especially the neurological. Neuritis is seen more frequently after sulfamethylthiazol and uliron, far less frequently after sulfathiazol, sulfapyridine and sulfanilamide — which is in agreement with the findings in animal experiments on the toxicity of these substances.

4. The sulfathiazol concentration of the blood and urine was examined in a number of the treated pneumonic patients, and the findings are compared to the corresponding findings for sulfamethylthiazol. Sulfathiazol was found to undergo acetylation in the blood and urine in a lesser degree than sulfamethylthiazol, and the latter was found to be excreted more slowly; the dispension of the values found in the blood was less for sulfathiazol than for sulfamethylthiazol.

5. Among 4 parturient women one showed a delayed absorption of sulfathiazol.

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# Reticuloendotheliose — Monozytenleukose.

## Mitteilung von 3 Fällen.

Von

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(Bei der Redaktion am 31. Januar 1942 eingegangen).

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Die Monozytenleukose ist eines der Leiden, dessen Stellung im haematologischen System in den letzten Jahrzehnten am stärksten diskutiert worden ist; dieses gilt besonders, wenn es sich um eine eventuelle aleukaemische Form handelt, wo man nicht nur den eventuellen Platz im Systeme diskutiert, sondern wo man sich auch über die Existenz des Leidens überhaupt in höchstem Grade uneinig ist. Die Frage steht mit dem Problem des Ursprungs der Monozyten und mit der Auffassung der Pathologie des reticuloendothelialen Systems in engem Zusammenhang, und wahrscheinlich bedeutet keine der bisher aufgestellten Theorien die endliche Lösung des Problems.

Ich habe Gelegenheit gehabt, 3 Fälle zu verfolgen, bei denen man die Diagnose einer Monozytenleukose gestellt oder in Erwägung gezogen hat. Da zwei der Fälle Erscheinungen aufweisen, die vom gewöhnlichen Bilde abweichen, und die zu diagnostischen Überlegungen Anlass geben können, erscheint es mir berechtigt, hierüber zu berichten, indem gerade die Mitteilung von derartigen atypischen Fällen vielleicht einmal dazu beitragen kann, das Verständnis gewisser Probleme der Erkrankung zu erleichtern.

Bevor ich meine Fälle beschreibe, möchte ich kurz die Monozytenleukose im Allgemeinen und die damit in Verbindung stehenden Probleme erwähnen, und dabei besonders die Verhältnisse berücksichtigen, die die hier vorliegenden Fälle berühren.

Der erste Fall von Monozytenleukose wurde von Reschad & Schilling im Jahre 1913 beschrieben. Diese Untersucher meinten durch den Nachweis dieser Leukoseform den Beweis dafür bekommen zu haben, dass die Monozyten eine haematologische Reihe für sich ohne nahe Verwandtschaft mit der myeloiden oder der lymphatischen Reihe ausmachten. Diese Auffassung fand nicht sogleich allgemeine Anerkennung, und besonders Naegeli nahm an, dass es sich nur um eine Abart der myeloiden Leukose mit (vorübergehender) Monozytose handelte. Nach und nach wurden jedoch zahlreiche Fälle von Monozytenleukose mitgeteilt, und die meisten Autoren nehmen jetzt an, dass es sich wirklich um eine besondere Krankheit mit gewissen charakteristischen klinischen und haematologischen Daten handelt. Nur wenige verneinen jetzt ihre Eksistenz. Aus Skandinavien wurden 5 Fälle berichtet. 3 von diesen wurden von Plum & Thomsen (1938) mitgeteilt, und in dieser Arbeit wird eine vorzügliche Übersicht über die Klinik und Haematologie der Erkrankung gegeben. Unter Hinweis auf diese Arbeit möchte ich nur die wichtigsten Symptome, so wie sie in mehreren Übersichtsarbeiten (Osgood u. a.) aufgestellt sind, erwähnen. 1). Zuweilen sind keine, und meist nur einzelne Lymphdrüsengruppen vergrössert, und dann in der Regel nur mässig. 2). Die Leber und die Milz sind oft nicht palpabel und in der Regel nur wenig vergrössert. 3). Wenn sich Gingivaaffektion findet, besteht diese oft in Nekrose (Forkner 1934). 4). Im Blute finden sich in der Regel eine vermehrte Anzahl von Leukozyten mit relativer und absoluter Monozytose und Vorkommen von unreifen Zellen der Monozytenreihe. Es ist charakteristisch, dass diese Vermehrung der Monozyten im Verhältnisse zu den normalen Zellen gewöhnlich nicht denselben Grad erreicht wie bei den anderen Leukosen, wo man z. B. bei einer lymphatischen Leukose 99 % Lymphozyten finden kann, während bei der Monozytenleukose oft wesentlich geringere prozentische Werte vorhanden sind. — Weiter fällt auf, dass neben den unreifen Monozyten oft unreife Zellen der myeloiden Reihe vorkommen. Gerade dieses Verhalten war Anlass zu Diskussionen über die Eksistenz einer selbstständigen Monozytenleukose. 5). Histo-

logisch findet man Infiltrationen von monozytähnlichen Zellen im Gewebe, die wesentlich perivasculär auftreten. — Eins der Hauptargumente Naegelis gegen die Eksistenz der Monozytenleukose ist die erwähnte Tatsache, dass man oft eine Reihe unreifer Zellen der myeloiden Reihe im peripheren Blute findet. Dieses Argument wird teilweise dadurch geschwächt, dass etwas ähnliches auch recht oft bei chronischer lymphatischer Leukose vorkommt. Das Argument wurde endgültig von Doan & Wiseman (1934) entkräftet, die bei einem Falle von Monozytenleukose zeigten, dass die Monozyten als die einzigen der vorkommenden Zellen nicht an den normalen rythmischen Schwankungen, denen die normalen Leukozyten unterworfen sind (Doan & Zerfas, 1927), teilnahmen, und dass ferner die Monozyten teils amitotische Zellteilung und teils Mitosen zeigten, welche oft pathologisch, d. h. unsymmetrisch, unter Bildung von ungleich grossen Kernen waren, wohingegen die myeloiden Zellen sich bezüglich der erwähnten Erscheinungen normal verhielten.

Hiernach sollte kein Zweifel darüber herrschen, dass der leukotische Prozess nur die Monozyten umfasst hat, während die myeloiden Zellen auf eine pathologische Einwirkung reagiert haben.

Schilling machte schon 1919 darauf aufmerksam, dass der wesentliche Unterschied zwischen Monozytenleukose und Monozytose auf infektiöser Basis in dem echten hyperplastischen, infiltrativen Wachstum der Monozyten bei der Leukose liegt.

Das wesentliche Problem, zu dessen Lösung die Monozytenleukosen vielleicht beitragen können, ist der Ursprung der Monozyten. Über diese Frage herrscht noch unter den verschiedenen Autoren grosse Uneinigkeit. Forkner hat nicht weniger als 19 verschiedene Meinungen über diese Frage gesammelt. Einer der Gründe dieser Verwirrung ist vielleicht, wie Nordenson anführt (1938): »Jetzt hat fast jeder Haematologe seine eigene Nomenklatur, und in den Zellenbezeichnungen herrscht eine unglaubliche Verwirrung». Es würde von Vorteil sein, wenn die Haematologen versuchten, eine gleichartige Nomenklatur einzuführen.

Aschoff & Kiyono (1914) waren die ersten, die die ruhenden Wanderzellen und die Endothelzellen in ein System, das Reticuloendothelialsystem, zusammenfassten, indem sie zeigten, dass gewisse Bindegewebszellen, die »Histiozyten», in vivo dazu im

Stande waren, Karminfarbkörner, welche in die Blutbahn injiziert wurden, zu phagozytieren. Die Untersucher meinten, dass die Histiozyten mit den Monozyten des Blutes identisch seien, und dass deshalb die Monozyten zu den Bindegewebszellen in genetischer Beziehung ständen. Pappenheim (cit. Schilling 1919) zeigte indessen, dass man selten bei den Monozyten des Blutes Phagozytose findet, und er schlug daher vor, dass es mehr als eine Art von Monozyten gäbe, nähmlich die eigentliche Monozyten und die Histiozyten.

Als nach und nach die Mitteilungen über beobachtete Fälle von Monozytenleukose häufiger wurden, begann auch das Studium des reticuloendothelialen Systems und der Monozyten, und vor allem das Studium eines eventuellen Zusammenhangs der Monozyten mit dem reticuloendothelialen System. Bei Nordenson (1939) findet sich eine ausführliche Beschreibung dieser Entwicklung, und ich möchte mich darauf beschränken, einzelne Erscheinungen, die für die Diskussion meiner Fälle von besonderer Bedeutung sein könnten, anzuführen.

Auf Grund der Auffassung, dass die Monozyten in dem reticuloendothelialen Gewebe gebildet werden, hat man die Monozytenleukose als eine Reticuloendotheliose bezeichnet (Dameshek 1930, 1933 u. a.). Es bestand jedoch grosse Uneinigkeit darüber, inwieweit die Monozyten aus der reticulären oder aus der endothelialen Komponente des Systems gebildet wurde, sowie auch über das gegenseitige Verwandtschaftsverhältnis zwischen den Zellen, die man bei der histologischen Untersuchung hyperplastisch fand. Man hat besonders diskutiert, ob man die Histiozyten als Stammzellen der Monozyten betrachten solle, oder ob sie nebengeordnete Zellen evt. mit gemeinsamen Ursprung seien. Thaddea & Bakalos (1939) haben die Theorie aufgestellt, dass die Stammzellen der Monozyten, welche sie Monoblasten und Promonozyten benennen, mit den Zellen, die man gewöhnlich Myeloblasten und Promyelozyten nennt, identisch seien. Sie lehnen die Bedeutung dieser Zellen für die Granulopoiese, jedenfalls unter normalen Verhältnissen, ab. Ein wichtiger Grund dieser Unübereinstimmungen liegt, wie u. a. Forkner und Nordenson hervorheben, in der fehlenden Einigkeit über die Nomenklatur. Es ist so keineswegs sicher, dass zwei Untersucher mit der Bezeichnung Histiozyten das gleiche meinen.

Man ist sich nicht vollständig darüber einig, ob die Monozytenleukose eine Reticulose ist. Levine und Schilling haben Fälle von Monozytenleukose beschrieben, bei denen keine wesentliche Proliferation des reticulären Gewebes gefunden wurde. Osgood (1937) hält die Bezeichnung Reticulose oder Reticuloendotheliose für die Monozytenleukose nicht für geeignet, da sie ein Wissen vortäuscht, das man nach seiner Meinung noch nicht besitzt. Nach Osgoods Auffassung wäre es genau so gerechtfertigt, die übrigen Leukosen als Reticuloendotheliosen zu bezeichnen, da alle Zellen des Blutes schliesslich von den multipotenten, mesenchymalen Gewebszellen, welche das reticuloendotheliale System ausmachen, abstammen. Forkner (1938) ist derselben Auffassung. Grosse Uneinigkeit besteht auch über den Begriff »aleukaemische Reticuloendotheliose» oder »aleukaemische Monozytenleukose». Unter dieser Bezeichnung wurden mehrere Fälle beschrieben (Letterer 1924, Clough 1932, Dameshek 1933 u. a.), bei denen man Proliferation des reticuloendothelialen Systems ohne gleichzeitig vorkommende Blutveränderungen gefunden hat. Andere Autoren (Levine 1934, Osgood 1937) lehnen diese Auffassung ab und machen darauf aufmerksam, dass es sich wahrscheinlich um atypische, septische Infektionen mit reticuloendothelialer Reaktion gehandelt hat.

Epstein (1925) hat als erster versucht, die Reticulosen zu systematisieren. Er erwähnt zwei Haupttypen: reine Reticulosen und assoziierte Reticulosen. Bei den erstgenannten ist Proliferation des reticuloendothelialen Gewebes ohne sichere Veränderungen des peripheren Blutes vorhanden, während die zweite Gruppe von derartigen Veränderungen begleitet ist (Monozytose, Lymphozytose etc.). Robb-Smith (1938) hat versucht, die Reticuloendotheliosen auf Grund des histologischen Befundes in den Lymphdrüsen einzuteilen. Er stellt ein sehr sinnreiches und sehr schematisches System auf, welches sicherlich das allergrösste histologische Spezialwissen fordert, um mit Erfolg durchgeführt zu werden. Hiernach gehören sämtliche Leukosen zu den Reticulosen, da sie zu den sogenannten »medullären Reticulosen» gehören, bei denen Proliferation des reticulären Gewebes, das mit dem Pulpagewebe der Lymphdrüsen in Verbindung steht, vorkommt. Dies stimmt insoweit mit der erwähnten Auffassung Osgoods überein.

Nordenson hat das reticuläre Gewebe besonders durch Knochenmarksbiopsien und durch intrasternale Injektion mit Tusche ein-

gehend untersucht. Er unterscheidet zwischen Monozytenleukose und Reticulose mit monozytärer Blutreaktion; in beiden Fällen kommt Proliferation des reticuloendothelialen Systems vor, diese ist jedoch bei den Leukosen nicht stark ausgesprochen. Er teilt drei Fälle von Reticulose mit, zwei acute und einen chronischen. Die acuten Fälle zeigen zum Teil monozytäre Blutreaktion, der chronische Fall nicht. Der Untersucher hat durch eine experimentelle Arbeit nachgewiesen, dass ein Teil der Blutmonozyten sowie auch ein Teil der Knochenmarksreticulumzellen nach intrasternaler Injektion mit Tusche diese phagozytieren, und er nimmt an, dass diese Monozyten von den phagozytierenden Reticulumzellen stammen. Bei den drei erwähnten Fällen von Reticulose findet man sehr deutliche Übergänge zwischen den Reticulumzellen des Knochenmarks und den Monozyten, die zum Teil das periphere Blut prägten. Nach Nordensons Meinung besteht also hier eine Wahrscheinlichkeit für die reticuläre Abstammung der Monozyten. Nordenson legt nach seiner historischen Besprechung des Monozytenproblemes fest, dass die Auffassung der Monozytengenese stark subjektiv geprägt ist, und dass das Problem sich schwerlich auf pathologisch-anatomischen Wegen lösen lässt, da die Methoden der Differenzierung zu grob sind. Er meint jedoch festlegen zu können, dass die Monozyten genetisch mit dem reticuloendothelialen System zusammengehören, und dass sie unter gewissen pathologischen Verhältnissen hieraus entstehen.

***Fall I.*** Frau, K. M. A., geb. 24/5 1892. Keine früheren Erkrankungen. Ein halbes Jahr vor der Einlieferung (d. h. im Juni 1940) war die Patientin »erkältet» mit Husten und Fieber. Sie wurde zu Hause mit 30 Tabletten Streptamid (Leo) (9 Gramm Sulfanilamid) behandelt. Sie war 6 Wochen bettlägerig. — Seitdem fühlte sie sich müde, konnte jedoch ihr Hauswesen besorgen.

Während des letzten Monats vor ihrer Einlieferung nahm ihre Müdigkeit stark zu. Es kam gleichzeitig zu Palpitationen und Dyspnoe bei der Arbeit, Schwindel und Kopfschmerzen; zuletzt Paraesthesien in Händen und Füssen und Trockenheit im Munde. Keine Dyspepsie. Kein Zeichen von haemorrhagischer Diathese.

Einlieferung in die medizinische Abteilung des Kreis- und Stadtkrankenhauses in Svendborg am 4/12 1940. Die Patientin war bei der Einlieferung sehr anaemisch. Auf den Waden fanden sich einige Ekkymosen, sonst kein Zeichen von haemorrhagischer Diathese. Volle Prothese im Munde. Zahnfleisch und Mandeln zeigten keine Abweichung vom normalen. Keine palpabeln Lymphdrüsen. Stethoscopia cordis et pulmonum zeigte

nichts Abnormes. Der Bauch war gross und adipös, die Leber nicht palpabel, während die Milz einen Fingerbreit unter dem Rippenrande palpabel war. Übrigens keinen abnormen Befund. Blutsenkungsreaktion (nach Westergreen) 100 mm; Wassermann-Kahn-Reaktion ÷.

Untersuchung des Blutes und des Sternalpunktates (vergl. Schema und spätere Beschreibung) deuteten auf eine Monocytenleukose. Am 9/12 wurde Bluttransfusion gegeben, 500 cm³. Am 10/12 trat starke Haematemesis auf, die nicht zum Stillstand gebracht werden konnte, sondern fortsetzte, bis der Tod am 11/12 eintrat.

***Sectionsbefund*** (durch den Autor). Die Leiche ist äusserst anaemisch. Es findet sich eine adhaesive Pleuritis auf beiden Seiten. Die Lungen sind etwas schwer und fest mit reichlichem Oedem, doch ohne Infiltrationen. Die Pericardhöhle fast total durch eine dicke, fibröse, adhaesive Pericarditis obliteriert. Die Leber ist vergrössert, 23 × 18 × 7 cm, fest, graubraun mit graubrauner Schnittfläche ohne besondere Zeichnung. Die Milz ist vergrössert, 17 × 12 × 5 cm, auf der Schnittfläche graurot, leicht cadaverös, ohne besondere Zeichnung. Die Nieren sind leicht vergrössert, auf der Schnittfläche blass grau mit hyperaemischer Zone am Übergang zwischen Cortex und Medulla. Im Mesenterium, im Ventriculus, in den Intestina und in pelves renum sind Petechien; im Ventriculus wurde Blut gefunden. Keine Vergrösserung der Lymphdrüsen.

***Mikroskopische Untersuchung*** (durch den Autor). *Die Nieren:* Am Übergange zwischen Cortex und Medulla findet sich Infiltration von Zellen mit reichlichem Protoplasma und grossem Kern mit losem Chromatinnetz, von ovaler oder mehr oder weniger eingekerbter und unregelmässiger Form, genau wie die im Blute zirkulierenden Monozyten. Keine Riesenzellen. Wenige Mitosen, einzelne Plasmazellen. In *der Leber* ist das Parenchym wohlerhalten. Von den Scheiden der Portagefässe ausgehend ist mässige Infiltration von Zellen, die genau den in den Nieren gefundenen Typenzellen entsprechen, vorhanden. Keine Riesenzellen. Einzelne Mitosen. In *den Lungen* sind die Alveolen überall mit Oedemflüssigkeit gefüllt die teils rein, teils mit grossen mononucleären Zellen gemischt ist. In den Septen sieht man, teils intra-, teils extravasal, einige Zellen, die den Typenzellen ähneln. Gleichzeitig sieht man intravasal eine Reihe von Riesenzellen vom Typus der Megakaryozyten. *Das Knochenmark* ist sehr zellreich. Die normalen Elemente sind in grossem Umfange von den beschriebenen Typenzellen verdrängt, es ist jedoch eine Anzahl von erythropoietischen Zellen, einzelne myeloide und wenige Plasmazellen vorhanden. Mehrere Riesenzellen vom Typus der Megakaryozyten. Wenige Mitosen. In *der Milz* ist die normale Struktur ganz von dem hyperplastischen Pulpagewebe ausgefüllt. Dieses besteht aus zahlreichen, sehr unregelmässigen Zellen, grösseren und kleineren, mit rundem bis ovalem Kern und zahlreichen »Typenzellen» mit unregelmässig geformtem oder eingekerbtem Kern. Mehrere Riesenzellen mit grossem, hellem, in der Regel rundem Kern von lockerer Netzstruktur und mit reichlichem Protoplasma. Mehrere Mitosen. In einer *Lymphdrüse* wird mässige Hyperplasie des Markes gefunden mit Bildung von Zellansammlungen, welche reichliches Protoplasma und einen

grossen, hellen Kern haben, der von schwankender, runder bis ovaler oder stark eingekerbter Form ist wie die Typenzellen. Ausserhalb dieser Ansammlungen findet sich normales, lymphatisches Gewebe. — In keinem der Organe wurde eine sichere Vermehrung des Reticulinnetzes gefunden, auch nirgends Hyperplasie oder Hypertrophie der Endothelzellen in den Capillaren oder in den Sinus.

Es handelt sich also um eine 48-jährige Frau, die ungefähr seit ½ Jahre an einer Erkrankung gelitten hat, die zum Schluss einen acuten Verlauf nahm und zum Tode führte. Das periphere Blutbild und die Knochenmarksbiopsie deuteten auf Monozytenleukose. Die mikroskopische Untersuchung der Organe bestätigte diese Diagnose, da infiltratives Wachstum monozytären Gewebes, hauptsächlich von den Gefässscheiden ausgehend, gefunden wurde.

***Fall II.*** Mann, C. J. C. L., geb. am 6/5 1877. Keine früheren Erkrankungen. 5/4—28/8 1931 Einlieferung in die staatliche Irrenanstalt in Viborg mit der Diagnose einer Psychosis psychogenica. Der Haemoglobinwert (Sahli) war damals 102 %. Keine Milz- oder Leberschwulst. 1937 begann der Patient unter Müdigkeit zu leiden, und der Arzt stellte Anaemie (Sahli 50 %) und Achylie fest.

Einlieferung in die med. Abteilung des Kreis- und Stadtkrankenhauses in Odense vom 17/1—25/2 1938. Man stellte hier fest, dass seine Milz bis zur Umbilicaltransversale reichte; bei der somatischen Untersuchung übrigens kein abnormer Befund. Wassermann-Kahn-Reaktion ÷. Blutdruck 150/100. Osmotische Resistenz leicht herabgesetzt, Blutsenkung (Westergreen) 70 mm, Sahli: 49 %, Leukozyten: 2240 mit »normaler Verteilung» (das Ausstrichpräparat nicht erhalten), Blutungszeit: 20 Min. Achylie. Man stellte die Diagnose Morb. Banti, und der Patient wurde in die chirurgische Abteilung überführt, wo man nach Bluttransfusion Splenektomie vornahm. Die Milz mass 29 × 11 × 4.5 cm, wog 670 g. Vgl. unten die histologische Untersuchung der Milz.

Nach der Entlassung befand sich der Patient einigermassen wohl, litt jedoch fortwährend an zunehmender Müdigkeit.

5/3—24/4 1939 wieder in die med. Abteilung wegen einer Bronchopneumonia dx. eingeliefert. Er wurde mit M & B 693 und acid. ascorbin. intravenös behandelt. Blutsenkung: 12—58—22 mm. Wassermann-Kahn—Reaktion ÷, Widal ÷. Untersuchung des peripheren Blutes vgl. Schema. Von Vergrösserung der Leber kein Zeichen. Fühlte sich bei der Entlassung wohl.

Seitdem fortwährend zunehmende Müdigkeit; eine Zeitlang war er bettlägerig mit Fieber bis zu 39°. Später etwas Hautjucken. Zu Blutungstendenz kein Zeichen.

Wurde wieder in die selbe Abteilung eingeliefert 13/7—25/7 1939. In dem Gesicht hatte er ein kleinpustulöses Exanthem und auf dem Rumpf ein petechiales. Paul-Bunnels Reaktion für Mononucleosis infect.: ÷. Die



*Abb. I. Monozyten von Sternalpunktat.* Fall II. × 1000.

Man sieht den unregelmässigen Kern mit Chromatinknötchen und Vacuolen. Diese Zellen sind für alle drei Fälle typisch.

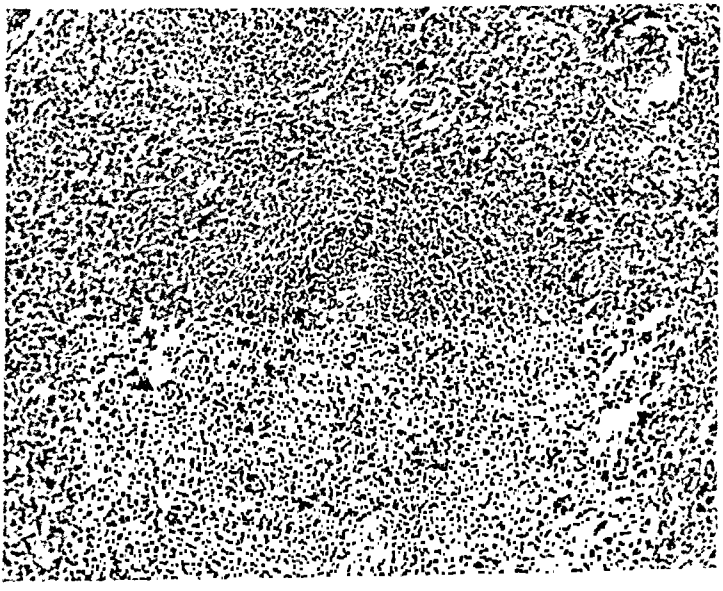


*Abb. II. Eine Milzfollikel.* Fall II. × 100.

Man sieht die normale Zentralpartei der Follikel, von einer helleren Zone abnormer Zellen umgeben.

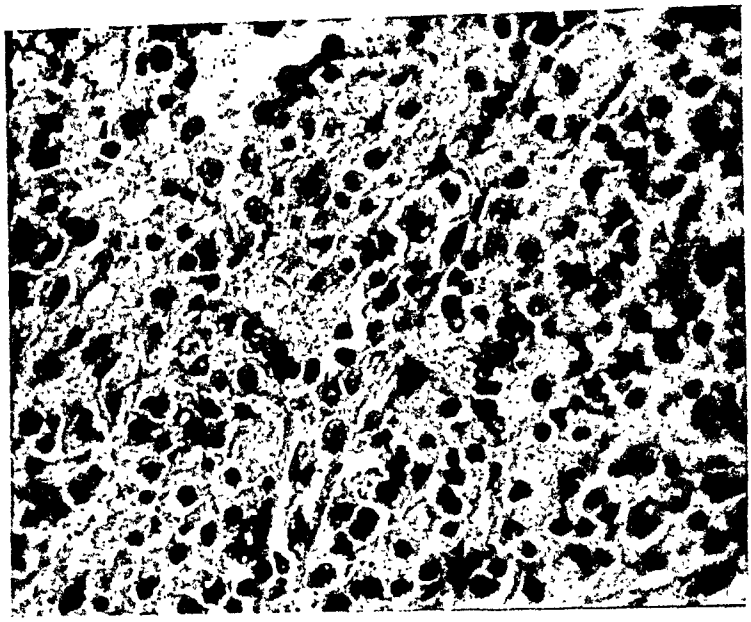


*Abb. III. Milzcapillar.* Fall II. × 450.
Mehrere hyperplastische Endothelzellen.

Untersuchung des peripheren Blutes und die Knochenmarksbiopsie deuteten auf Monozytenleukose (vgl. Schema und spätere Beschreibung). Der Patient wurde deshalb in die Radiumstation in Odense überführt wo er vom 25/7—23/8 lag. Er war bei der Einlieferung mager, leicht anaemisch. Im Gesicht und auf dem untersten Teil des Rumpfes waren zahlreiche kleine, gelblichbraune Papeln und einzelne Petechien vorhanden. In der Mundhöhle kein abnormer Befund, bes. keine Schwellung des Zahnfleisches und keine Nekrosen. Der Schlund: die Tonsillen nicht vergrössert. Die Leber reichte von der Mitte der linken Curvatur bis Spina iliaca anterior superior; die Oberfläche war glatt, und das Organ fühlte sich hart an. Auf beiden Seiten des Halses, in der rechten Achselhöhle und in beiden Leisten waren wenige verschiebbare, weiche, nicht schmerzende Drüsen fühlbar. Blutuntersuchung und Sternalpunktur vgl. Schema und spätere Beschreibung. Es wurden 22 Röntgenuniversalbestrahlungen von je 6 r gegeben. Die Temperatur schwankte auf uncharakteristische Weise zwischen 37° und 38.5°.

Der Patient befand sich bei der Entlassung wohl, wurde aber bald müde und matt. Der Arzt des Patienten erklärte, dass dieser einige Zeit darauf an einer exsudativen Pleuritis erkrankte. Er wollte sich sehr ungern wieder einliefern lassen, weshalb man (am 20/10 1939) bei ihm einen Besuch ablegte, um eine Blutprobe zu entnehmen (vgl. Schema).

Am 25/11 1939 wurde der Patient wieder in die Radiumstation in Odense eingeliefert, der Tod trat aber unmittelbar nach der Einlieferung ein; eine Probe des peripheren Blutes konnte man deshalb nicht entnehmen.

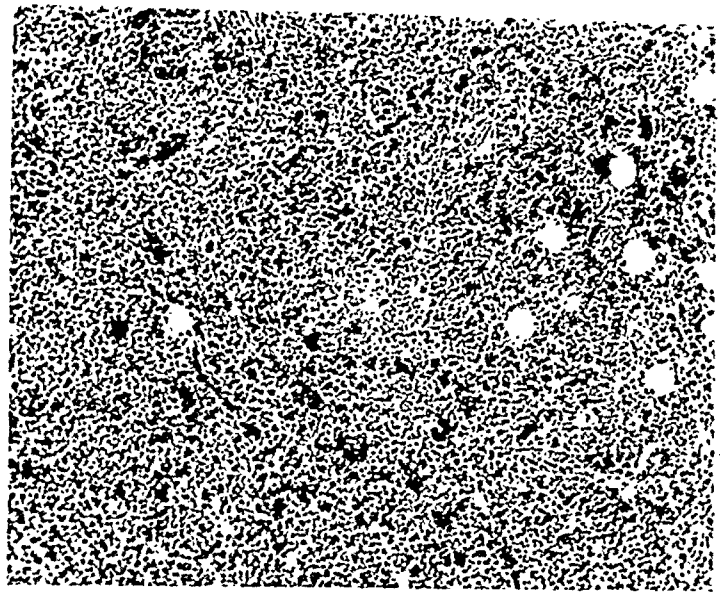


*Abb. IV. Knochenmark.* Fall II. × 100.
Kräftige Hyperplasie.

3 Stunden post mortem führte man eine Sternalpunktur aus. Hierin waren die Zellen recht wohl bewahrt.

***Sectionsbefund*** (Prosector J. Vesterdal Jørgensen). Pleurae: verbreitete lose Bindegewebsadhaesionen auf beiden Seiten. Ziemlich reichliche gelbliche, seröse Flüssigkeit. Lungen: gross, schwer, hyperaemisch und oedematös. Keine Infiltrate, spez. keine Zeichen von Tuberkulose oder Metastasen. Die Hilusdrüsen nicht vergrössert. Das Herz: kein besonderer Befund, spez. keine Endocarditis. Die Bauchspeicheldrüse normal; an ihrer Unterseite eine Lymphdrüse von der Grösse einer grünen Wallnuss, die auf der Schnittfläche hell gelblich, etwas fest ist. Die Leber stark vergrössert, Gewicht 4800 g. Die Oberfläche glatt. Die Konsistenz weich. Auf der Schnittfläche ist die Zeichnung bald ausgelöscht, bald wie vergröbert. Die Gallenblase vergrössert mit ca. 100 fazettierten Steine von Erbsengrösse. Die Nieren voluminös. Die Kapsel leicht abzulösen. Die Oberfläche glatt mit normaler Zeichnung, die in der linken Niere jedoch leicht verwischt und etwas heller ist als in der rechten (an leukaemisches Infiltrat erinnernd). Das Knochenmark locker, graurot.

***Mikroskopischer Befund*** (durch den Autor). *Die Nieren:* verbreitete Degeneration des Parenchymes mit peritubulärem Oedem. In ausgedehnten Ansammlungen Infiltration mit reticulärem, sehr zellreichem Gewebe. Die Kerne dieser Zellen sind meist recht gross mit feinmaschigem Chromatinnetz und deutlicher Kernmembran; es kommen aber auch kleinere und etwas dunklere Kerne vor. Viele der Kerne zeigen die gleiche Form wie die der im Blute und in dem Knochenmark nachgewiesenen Monozyten:

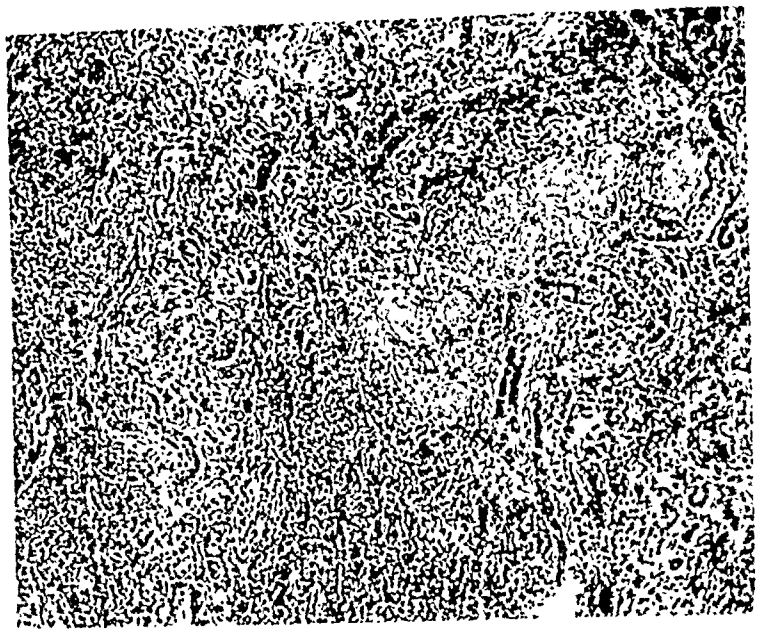


*Abb. V. Niere.* Fall II. × 100.
Leukaemische, peritubuläre Infiltration.

eine stark eingekerbte und unregelmässige. Silbergefärbtes Präparat a. m. Foot zeigt ausgesprochene Vermehrung des Reticulins in den Infiltraten. — Starke Infiltration von genau der gleichen Art wie in dem Nierenparenchym findet sich in einem perirenalen Fettgewebe. *Die Lungen:* starke Hyperaemie der Capillaren. Die Alveolen sind mit Exsudatflüssigkeit gefüllt. Die Septa sind sehr zellreich, die Zellen sind von der gleichen Art wie die bei den Nieren beschriebenen »Typenzellen». Um einige der grösseren Gefässe herum ausgesprochene Infiltration von »Typengewebe». Keine sichere Reticulinvermehrung. An einzelnen Stellen in den Capillaren kommt Hypertrophie der Endothelzellen mit grossem, gedehnt-ovalem Kern und reichlichem Protoplasma vor. Einige Riesenzellen mit unregelmässigem Kern (Megakaryozyten). *Die Leber:* verbreitete Degeneration des Parenchyms in grossen Teilen. Von den Scheiden der vena porta und arteria hepatica ausgehend findet man überall starke Infiltration des Parenchyms mit Typengewebe mit den charakteristischen Kernen und mit Reticulinvermehrung. Ausserdem wenige segmentkernige Leukozyten und Lymphozyten und einzelne Plasmazellen. Einzelne Mitosen kommen vor. Keine Riesenzellen. Starke Hyperaemie der Capillaren. Hier und dort Hypertrophie der Endothelzellen in den Capillaren. *Das Knochenmark* ist ausserordentlich zellreich. Normale Knochenmarkszellen fehlen fast gänzlich, sie sind von zahlreichen Typenzellen ersetzt mit grossem, hellem Kern von schwankender Grösse, von ovaler und unregelmässiger bis stark eingekerbter und gekrümmter Form. Wenige eosinophile Zellen. Mehrere Riesenzellen mit grossem, ganz unregelmässigem Kern, welche vollstän-

dig an Megakaryozyten erinnern. *Das Blut* in den Gefässen der Organe und aus einem fixiertem Koagulum einer grossen Vene: von kernhaltigen Zellen gefüllt, worin die Kerne grösser oder kleiner sind, hell mit lockerem Chromatinnetz, von ovaler oder unregelmässiger Form wie die beschriebenen Typenzellen. *Die Schilddrüse und Nebennieren:* nichts Abnormes. *Die Milz* (Operationspräparat 21 Monate vor dem Tode): Die Follikelstruktur erhalten. Die Follikeln etwas hyperplastisch. Die zentralen Teile der Follikeln sind normal, oft mit Keimzentren. Man sieht jedoch eine deutliche Abnormität peripher in den Follikeln, indem die Zellen grösser als normal werden mit grossem, hellem Kern mit losem, deutlich gezeichnetem Chromatin und deutlicher Kernmembran. Die Kerne sind von recht schwankender Form, einige von ovaler oder runder, andere von grösserer und unregelmässigerer Form. Das Pulpagewebe ist ebenfalls hyperplastisch mit deutlicher Vermehrung der Zellenanzahl. Die Kerne hierin von schwankender Form wie oben beschrieben. Ausserdem viele Plasmazellen. Das Reticulin ist deutlich vermehrt. An zahlreichen Stellen sieht man die Endothelzellen hyperplastisch mit reichlichem Protoplasma an der Capillarwand entlang gelagert und einem Kern, vergrössert, langgedehnt oval mit dünnem, feinem Chromatinnetz. Man kann nicht mit Sicherheit feststellen, ob eine Abstossung dieser Zellen in die Blutbahn stattfindet, obgleich dies an mehreren Stellen der Fall zu sein scheint. — Mehrere Mitosen kommen vor. Nur ganz einzelne der Pulpazellen gleichen Monozyten, indem doch der Kern in der Regel nicht so unregelmässig, eingekerbt und gewunden ist wie in diesen. Keine Hyperaemie in den Sinus oder in den Gefässen. *Lymphdrüsen:* Ausgesprochene Hyperplasie des Markgewebes mit Verdrängung von Sinus und Follikeln. Das hyperplastische Gewebe besteht zum grössten Teil aus Zellen mit recht reichlichem Protoplasma und einem Kern von schwankender Grösse, meist recht gross mit losem Chromatinnetz, deutlicher Kernmembran. Zahlreiche Kerne sind sehr unregelmässig, gekrümmt und eingekerbt wie Typenzellen. Einzelne Riesenzellen mit grossem, unregelmässigem Kern und mehrere Plasmazellen kommen vor. An einzelnen Stellen deutliche Hypertrophie des Capillarendothels. — In einer der Drüsen finden sich die von Tuberkeln bekannten Riesenzellen mit typischer, peripherer Lagerung der zahlreichen Kerne; es fanden sich jedoch keine Tuberkelbazillen.

Es handelt sich um einen 62-jährigen Mann, dessen Erkrankung einen chronischen Verlauf hatte. 21 Monate vor dem Tode wurde er wegen einer schweren Splenomegalie einer Splenektomie unterzogen. Kurz darauf entwickelte sich ein haematologisches Bild, welches auf Monozytenleukose deutete. Das Sectionsmaterial scheint diese Diagnose zu bestätigen, indem sich in verschiedenen Geweben infiltratives Wachstum monozytären Gewebes fand.

***Fall III.*** Mann H. P. L. A. geb. am 14/9, 1897. Keine früheren Erkrankungen, von einer Dyspepsie, welche seit seinem 25. Jahre andauerte, abgesehen. 4 Monate vor der Einlieferung begann das jetzige Leiden mit zunehmender Müdigkeit und Gewichtverlust. Gleichzeitig verschlimmerte sich die Dyspepsie. Keine Melaena oder Haematemesis.

Einlieferung in die chirurgische Abteilung A des Kreis- und Stadtkrankenhauses in Odense am 18/1 1940. Röntgenbild des Magens und Darmkanals: kein Zeichen von Cancer. Wassermann-Kahn-Reaktion ÷. Sahli: 42 %, Erythrozyten: 1.16 Mill. Index color. 1.81. Blutsenkungsreaktion (Westergren): 120 mm, Faeces: keine occulte oder manifeste Blutung.

Wurde am 9/2 in die med. Abteilung B überführt. Blutsenkung: 161—180 mm. Blutdruck: 130/80. Urin: nichts Abnormes, spez. keine Bence-Jones' Protein. Venülenblut: kein Wachstum. Paul-Bunnel's Reaktion für Mononucleosis infect.: ÷. Röntgenfoto der Lungen und diverser Knochen: kein abnormer Befund. Blutuntersuchung: vgl. Schema. Es wurde Intricula 2 Röhren täglich und inj. Exhepa fort. 2 cm³ 2mal wöchentlich gegeben. Am 21/2 wurde Bluttransfusion gegeben (450 cm³). Wegen des Fundes bei der Sternalpunktur, welcher auf Monozytenleukose deutete (vgl. Schema und spätere Beschreibung), wurde er am 22/2 1940 in die

Radiumstation in Odense überführt. Er war damals stark anaemisch. Im Gesicht und auf dem Rumpfe fand sich ein verbreitetes maculopapulöses Exanthem mit Rötung und Infiltration in verstreuten Flecken. Der Patient hatte schon immer eine »unreine» Haut, das Exanthem soll sich jedoch in den letzten Monaten verschlimmert haben. — Kein Zeichen von haemorrhagischer Diathese. Atrophie der Papillen der Zunge, deren Oberfläche stark gefurcht war. Das Zahnfleisch im unteren Teil des Mundes war etwas succulent, doch ohne Haemorrhagien oder Nekrosen. Die Schleimhäute zeigten übrigens nichts Abnormes. Keine palpabeln Lymphdrüsen. Stethoscopie der Lungen und des Herzes normal. Leber und Milz nicht fühlbar. Keine Ascites. An den Extremitäten nichts Abnormes. Am 21/2 wurde eine inguinale Lymphdrüse für die Biopsie entfernt. Diese ergab ein Bild, »welche für keine bestimmte Systemkrankheit charakteristisch ist, sondern am stärksten auf eine beginnende Lymphogranulomatosis oder Reticulosis deutet» (Prosector J. Vesterdal Jørgensen). — Es wurden 16 Universalröntgenbestrahlungen von je 6 r gegeben. Man setzte die Eingabe von Exhepa fort., vom 12/3 2 cm³ 2mal täglich fort. Die Temperatur schwankte auf uncharakteristische Weise zwischen 37° und 39°. Der Patient verfiel langsam und starb am 4/4 1940.

***Sectionsbefund*** (Prosector J. Vesterdal Jørgensen). Die Lungen zeigen moderates Oedem, sonst keinen abnormen Befund. Die Leber: nicht vergrössert, etwas blass mit gelblichgrauem Schimmer. Die Milz bis zu ungefähr dem doppelten vergrössert; auf der Schnittfläche ist die Pulpa gleichförmig graurot, mässig verfliessend ohne besondere Zeichnung, spez. sind die Follikeln nicht sichtbar. Die Lymphdrüsen zeigen nichts makroskopisch Abnormes. Die Nieren etwas blass, ziemlich gross, übrigens aber

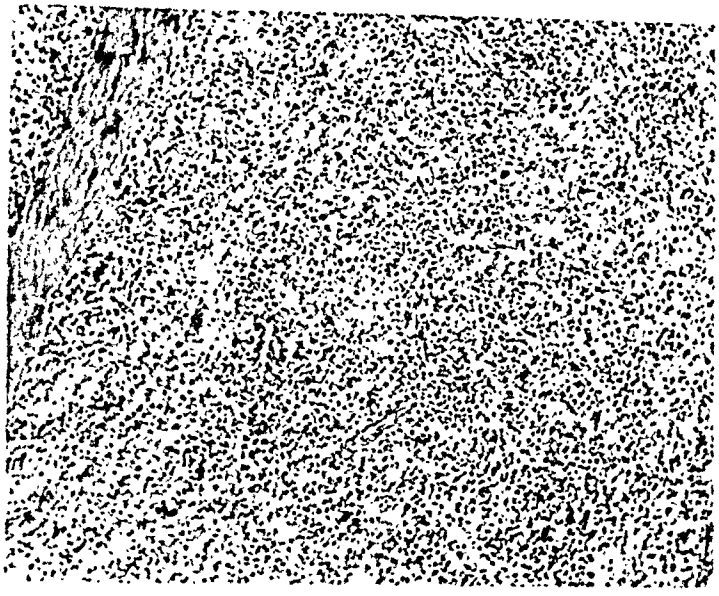


*Abb. VI. Milz.* Fall III. × 100.
Hyperplasie des Pulpagewebes.

ohne makroskopisch sichtbare Veränderungen. Die Schnittfläche des Knochenmarks ist graulich. — Sonst kein abnormer Befund.

***Mikroskopische Untersuchung*** (durch den Autor). *Die Leber:* ausgebreitete Nekrose der zentralen Teile der Acini, sonst nichts Abnormes. In *den Lungen, den Muskelgeweben* und *den Nieren* nichts Abnormes. Das Knochenmark ist ausserordentlich zellreich mit Hyperplasie recht grosser Zellen mit grossem Kern, dessen Grösse etwas schwankend ist, und dessen Form von oval bis nierenförmig variiert; ausserdem kommen Zellen mit unregelmässigem Kern vor, welche ganz den bei den Knochenmarksbiopsien gefundenen Monozyten ähneln. Einzelne Mitosen. Die normalen Knochenmarkselemente fehlen fast gänzlich, es kommen jedoch einzelne kleine Lymphozytenansammlungen und Ansammlungen von erythropoietischen Zellen und wenige Plasmazellen vor. Einige Megakaryozyten, keine anderen Riesenzellen. Die »Typenzellen» ähneln ganz denjenigen von Fall I und II. *Die Milz:* Die Follikelstruktur ist teilweise ausgefüllt, indem die Follikeln kleiner als normal sind und gegen das umgebende Gewebe, wo man Hyperplasie von Zellen findet, weniger deutlich hervortreten. Diese zeigen unnormal grosse Polymorphie, da ausser den normalen Elementen grössere Zellen mit grossem, ovalem oder rundem Kern mit lockerer Chromatinstruktur und relativ sparsamem Protoplasma vorkommen. Nur wenige Riesenzellen mit unregelmässigem Kern. Wenige Plasmazellen. Ziemlich viele Mitosen. Nur wenige »Typenzellen»; sparsame Vermehrung des Reticulins. An mehreren Stellen kommt Hyperplasie der Endothelzellen der Capillaren vor, wie bei Fall II beschrieben wurde. Keine Hyperaemie. *Die Lymphdrüsen:* Hyperplasie des Markgewebes mit reichlichem,

losmaschigem Reticulinnetz. Kompression von Sinus und Follikeln. Im Markgewebe kommen ein Teil Lymphozyten und zahlreiche grössere Zellen mit losmaschigem Chromatin vor. Der Kern dieser Zellen ist meist rund oder oval, nur in einzelnen eingekerbt. Ausserdem kommen zahlreiche grosse Zellen mit grossem Kern von lockerer Netzstruktur und mit reichlichem Protoplasma vor, worin reichliches, schwarzbraunes Pigment vorhanden ist. Viele dieser Zellen sind besonders gross mit zwei oder mehreren unregelmässig gelagerten Kernen.

Es handelt sich um einen 42-jährigen Mann mit einem recht acuten Verlauf der Erkrankung. Die Knochenmarksbiopsien deuteten auf Monozytenleukose; bei der mikroskopischen Untersuchung des Sectionsmaterials wurde diese Diagnose jedoch nicht bestätigt.

## Blutpraeparate und Knochenmarksbefund.

Morphologisch waren die Blut- und Sternalpraeparate der 3 Fälle sozusagen gleich und können zusammen beschrieben werden.

Die Monozyten ähneln den Monozyten des gewöhnlichen Blutes. Das Protoplasma war reichlich, hell blau-grau mit feinstaubiger Azurgranulierung. In mehreren der Monozyten fanden sich Vacuolen. Der Kern war gross, unregelmässig geformt und eingekerbt, und, für die Monozyten typisch, von deutlich »voluminösem« Gepräge. Das Chromatin feinmaschig, nicht ganz regelmässig mit gröberen Knötchen. Der Kern, besonders bei Fall II, meist unregelmässiger und gewundener als in den normalen Monozyten, oft von ganz bizarrer Form.

Die Promonozyten hatten runden oder etwas eingekerbten Kern. Die Chromatinstruktur war fein, jedoch nicht so regelmässig wie bei den Promyelozyten, und es kamen wie in den Monozyten Knötchen vor. Einige der Kerne hatten 1—4 deutliche, hellblaue Nucleoli. Das Protoplasma war weniger reichlich als das der Monozyten, mehr rein blau mit feiner netzartiger Struktur und mit wenigen bis zahlreichen recht groben Azurkörnchen, die bisweilen, speziell bei Fall I, die Zellen den Promyelozyten sehr ähnlich machten. Oft fanden sich Vacuolen.

Die Chromatinstruktur der Monoblasten war feiner als die der Promonozyten aber nicht so regelmässig wie die der Myeloblasten, wie die früher genannten Zellen zeigten die Monoblasten unregelmässige Chromatinverdichtungen, Knötchen. In den meisten

**Tabelle 1.** *Schema der Bluntersuchungen.*

| Fall Nr. | Dato | Blutsenkung in mm/Stunde nach Westergreen | Sahli, % | Erythrozyten in Millionen | Thrombozyten | Leukozyten pr mm³ | Myeloblasten % | Promyelozyten % | Myelozyten % | Metamyelozyten % | Stabkernige % | Segmentkernige, neutrophile % | Segmentkernige eosinophile % | Segmentkernige basophile % | Monoblasten % | Promonozyten % | Monozyten % | Lymphozyten % | Normoblasten % | Uncharakteristische % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 5/12—40 | 100 | 30 | 1.58 | — | 93920 | — | — | 1 ²/₃ | 3 | 6 ⅓ | 39 ⅓ | — | ⅓ | 1 ⅓ | 6 | 23 ²/₃ | 16 ²/₃ | 1 | ²/₃ |
| | 9/12—40 | — | 20 | — | — | 140640 | — | — | ⅓ | 1 ²/₃ | 15 | 28 ²/₃ | — | — | 3 ²/₃ | 9 ⅓ | 27 ²/₃ | 13 | ⅓ | ⅓ |
| II | 19/1 —38 [1] | 70 | 49 | — | — | 2240 | »Normale Verteilung« | | | | | | | | | | | | | |
| | 21/3 —39 [1] | 58 | 54 | 3.28 | — | 26000 | — | — | — | — | — | 73 | — | — | — | — | 14 | 13 | — | — |
| | 11/4 —39 [1] | 22 | 63 | 3.82 | — | 34360 | — | — | — | — | — | 48 | — | 1 | — | — | 29 | 22 | — | — |
| | 14/7 —39 [1] | — | 70 | 4.00 | — | 102300 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 15/7 —39 | — | — | — | — | — | ²/₃ | 3 | 3 | 10 ²/₃ | 11 | 38 | — | ⅓ | 1 ²/₃ | 5 ²/₃ | 16 ⅓ | 7 ²/₃ | 1 ²/₃ | ⅓ |
| | 24/7 —39 [1] | — | — | — | — | 80720 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 26/7 —39 | 2 | 80 | — | — | 72000 | — | ⅓ | 1 ⅓ | 5 ²/₃ | 7 ⅓ | 41 | ²/₃ | ⅓ | 2 ²/₃ | 2 | 30 | 7 ²/₃ | ⅓ | ²/₃ |
| | 11/8 —39 | — | 80 | — | — | 35800 | — | — | — | 1 ²/₃ | 9 | 56 | ²/₃ | ²/₃ | 2 ⅓ | 2 | 17 ²/₃ | 8 | 2 | — |
| | 12/10—39 | — | — | — | — | 20280 | — | — | ⅓ | 1 ²/₃ | 3 ²/₃ | 8 | 7 ⅓ | 3 | 7 ⅓ | 2 ⅓ | 50 ⅓ | 14 ⅓ | — | ²/₃ |
| III | 20/1 —40 [1] | 120 | 42 | 1.16 | — | 4720 | — | — | — | — | — | 76 | — | — | — | — | 8 | 16 | — | — |
| | 10/2 —40 [1] | 161 | 35 | 1.08 | — | 5800 | — | — | — | — | — | 68 | — | — | — | — | 6 | 26 | — | — |
| | 20/2 —40 [1] | 180 | 22 | 0.67 | — | 3840 | — | — | — | — | — | 60 | — | — | — | — | 1 | 39 | — | — |
| | 21/2 —40 | | | | | Transfusio sanguinis, 450 cm³ | | | | | | | | | | | | | | |
| | 21/2 —40 | — | 27 | 1.80 | — | 4440 | — | — | ⅓ | — | 1 ⅓ | 65 ²/₃ | — | — | 2 ⅓ | 3 ²/₃ | 6 | 20 ²/₃ | — | — |
| | 26/2 —40 | 120 | 19 | — | — | 3200 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 6/3 —40 | — | 20 | — | — | 3160 | — | — | ½ | — | 1 | 73 | — | — | 2 | 2 ½ | 4 | 17 | — | — |
| | 27/3 —40 | — | 11 | — | — | 1240 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | | | | | | 52000 | | | | | | | | | | | | | | |

[1] Nicht vom Autor untersucht.

**Tabelle 2.**

*Schema der Sternalpunkturen.*

| Fall Nr. | Dato. | Myeloblasten % | Promyelozyten % | Myelozyten neutr. % | Myelozyten eosin. % | Metamyelozyten neutr. % | Metamyelozyten eosin. % | Stabkernige neutr. % | Segmentkernige neutr. % | Segmentkernige eosin. % | Segmentkernige basoph. % | Monoblasten % | Promonozyten % | Monozyten % | Plasmazellen % | Lymphozyten % | Proerythroblasten % | Erythroblasten % | Normoblasten % | Megaloblasten % | Megakaryozyten | Reticulumzellen % | Uncharakteristische % | Anzahl von kernhaltigen Zellen pr mm³ des Punktates |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 9/12—10 | 0.2 | 0.6 | 5.2 | — | 7.2 | — | 11.8 | 24.8 | — | — | 5.0 | 10.4 | 21.8 | — | 8.2 | 0.2 | 1.6 | 2.2 | ÷ | + | — | 0.8 | 25:12:10 |
| II | 15/7 —39 | 0.4 | 1.0 | 5.2 | — | 16.8 | — | 16.8 | 29.4 | 0.2 | — | 2.4 | 3.6 | 15.0 | — | 5.2 | 0.2 | 1.0 | 2.4 | ÷ | + | — | 0.4 | — |
| | 26/7 —39 | 0.6 | 0.4 | 3.4 | — | 7.8 | — | 11.2 | 35.6 | 0.2 | 0.2 | 2.8 | 1.8 | 28.2 | — | 4.0 | 0.2 | 1.0 | 2.4 | ÷ | + | 0.2 | — | 70000 |
| | 25/11—39[1] | 0.2 | 0.8 | 7.8 | — | 10.0 | — | 4.6 | 10.2 | — | — | 11.0 | 9.0 | 35.0 | — | 2.0 | 0.4 | 3.2 | 5.2 | 0.2 | + | 0.2 | 0.2 | — |
| III | 13/2 —40 | 0.4 | 0.6 | 9.8 | 0.4 | 10.0 | 0.4 | 2.0 | 11.6 | 0.2 | — | 8.8 | 8.6 | 38.2 | 0.2 | 3.2 | 0.2 | 1.2 | 3.0 | 1.0 | + | — | 0.2 | — |
| | 6/3 —40 | 0.4 | 0.6 | 9.4 | 0.4 | 8.2 | 0.2 | 7.6 | 28.0 | 0.2 | — | 4.8 | 4 | 23.4 | 0.2 | 2.6 | 1.0 | 3.2 | 4.0 | 1.4 | + | — | 0.4 | — |

[1] Punktur 3 Stunden nach dem Tode vorgenommen.

Monoblasten fanden sich 1 oder mehrere Nucleoli. Das Protoplasma war rein blau ohne sichere Granulation, aber mit feiner, netzähnlicher Zeichnung. Oft Vacuolen. Keine der Zellen zeigten Phagozytose. Bei Oxydasenfärbung wurden die Monozyten schwach oxydase-positiv gefunden. Supravitalfärbung wurde nicht vorgenommen.

Die Erythrozyten zeigten bei allen Fällen deutliche Aniso-poikilozytose (bei Fall I am schwächsten) und bei Fall III wurde mässige Megalozytose gefunden.

Die quantitativen Verhältnisse in den Blutpraeparaten ergeben sich aus der *Tabelle I.* Fall I zeigte den typischen Befund bei Monozytenleukose mit hoher Leukozytenanzahl und zahlreichen Monozyten, Promonozyten und Monoblasten. Der Befund zeigte wie erwähnt, dass diese Zellen nicht absolut vorherrschend waren, so wie es die myeloiden Zellen bei der myeloiden und die lymphatischen bei der lymphatischen Leukose sind. Es kamen wenige unreife myeloide Zellen vor. Bei Fall II fand man vor der Splenektomie starke Leukopenie (Milzhemmung?). Danach stieg die Anzahl der Leukozyten bis zu leukaemischen Höhen, um darauf wieder etwas zu fallen (Röntgenwirkung?). Zunehmendes Vorherrschen von monozytären Zellen und abnehmende Mengen von unreifen myeloiden Zellen, die zu keinem Zeitpunkt besonders hohe Werte erreichten, wurde beobachtet, Es war bemerkenswert, dass der Haemoglobinwert in diesem Falle zu keiner Zeit besonders niedrig und zwar zum Schluss fast normal war. Bei Fall III sah man während des ganzen Verlaufes niedrige Leukozytenanzahl, und die Verteilung der Zellen zeigte nichts Abnormes.

Die Blutsenkungsreaktion war bei Fall I und III hoch, bei Fall II nur am Anfang hoch, bei der letzten Untersuchung aber normal.

Die quantitativen Verhältnisse in den Sternalpunktaten ergeben sich aus der *Tabelle II.* Charakteristisch für alle Fälle war eine starke Vermehrung der monozytären Zellen; alle Praeparate zeigten das gleiche Gepräge von monozytärer Hyperplasie wie bei Monozytenleukose. Die übrigen Zellwerte waren entsprechend herabgesetzt, alle Fälle zeigten jedoch besonders starke Lymphopenie. Bei Fall III waren einige typische Megaloblasten, was der leichteren Megalozytose im peripheren Blute entspricht, vorhanden. Die Anzahl der Megaloblasten erreichte jedoch bei weitem nicht die hohen Werte, die man bei Anaemia perniciosa sieht.

## Besprechung der Ergebnisse.

Der ***Fall I*** war eine 48-jährige Frau. Ihre Erkrankung entwickelte sich im Anschluss an eine »Erkältung», welche infolge des Sectionsfundes wahrscheinlich eine Pleuritis oder Pericarditis war; in der Anamnese sonst keine früheren Erkrankungen, welche die Pleura- und Pericardieadhaerancen erklären könnten. Das todbringende Leiden hatte anfangs einen schleichenden Verlauf ohne besondere Symptome, im letzten Monat einen sehr akuten Verlauf. Bei der Einlieferung glich der Fall vollständig einer Leukose und entsprach ausgezeichnet dem Bilde einer Monozytenleukose. Hier ist jedoch zu bemerken, dass keine Affektion des Zahnfleisches vorhanden war, was sonst charakteristisch sein soll. Der Befund bei der Untersuchung des peripheren Blutes ergab die Diagnose einer Monozytenleukose, da Vermehrung der Monozyten vorkam, und da die vorhandenen unreifen Zellen morphologisch mit den Monozyten nahe Verwandtschaft zeigten, hingegen nicht mit den myeloiden Zellen, welche auch in etwas vermehrter Menge vorkamen. Die Monozyten zeigten pathologische Verhältnisse, während die myeloiden Zellen morphologisch vollständig normal waren. Dass die Monozyten keinen grösseren Teil der Zellen ausmachten, stimmt mit den Beobachtungen in der Litteratur (Levine 1934 u. a.) gut überein. Die Untersuchung des Sternalpunktates bekräftigte die Diagnose, indem hier bei den Monozyten und den unreifen Zellen das gleiche pathologische Verhalten vorkam wie in dem peripheren Blute, während die übrigen Zellen, von Lymphopenie abgesehen, keinen abnormen Befund zeigten. Die mikroskopische Untersuchung des Sectionsmaterials liess typische leukaemische Erscheinungen erkennen, in genauer Übereinstimmung mit früheren Beschreibungen von Monozytenleukose. In den Organen fand sich ausgesprochene Infiltration mit monozytärem Gewebe, besonders perivasculär. In der Milz und in den Lymphdrüsen schienen die leukaemischen Veränderungen von dem Reticulumgewebe des Pulpagewebes auszugehen, sonst ergab sich kein Befund, welcher mit Sicherheit andeuten könnte, von wo das leukaemische Gewebe ausging. In keinen der untersuchten Organen kam Hyperplasie des Endothels vor. — Es handelt sich ohne jeden Zweifel um einen Fall von subakuter Monozytenleukose.

Der ***Fall II*** war ein 62-jähriger Mann, dessen Erkrankung einen eigentümlichen Verlauf zeigte, anfangs mit einer Milzgeschwulst, die ausser einer bedeutenden Leukopenie von keinen charakteristischen Symptomen begleitet war. Bei der Untersuchung der operativ entfernten Milz fand man eine ausgesprochene Reticulose und eine ausgesprochene Hyperplasie der Sinusendothelzellen. Im Laufe der nächsten 15 Monate entwickelte sich ein Bild, welches klinisch einer Leukose glich; bei der Untersuchung des Blutes und des Sternalmarkes kamen ausgesprochene Veränderungen vom gleichen Typus wie bei Monozytenleukose vor. Die Leukozytenanzahl stieg in diesem Zeitpunkt bis zu 102,300. Gleichzeitig war eine mässige Anaemie vorhanden. Während und nach einer leichten, universellen Röntgenbehandlung schwanden die haematologischen Veränderungen etwas, eine ausgesprochene Vermehrung der monozytären Zellen und ihrer Vorstadien blieb indessen. Die Anaemie nahm etwas ab, die Blutsenkung wurde normal; das Allgemeinbefinden wurde jedoch allmählich schlechter, und der Patient starb 21 Monate nach der Splenektomie. Postmortale Untersuchung des Knochenmarkspunktates zeigte eine Vermehrung der monozytären Zellen bis zu 55 %. Das letzte Blutbild, 6 Wochen vor dem Tode, liess nur leichte Leukozytose erkennen, dagegen die bisher stärkste relative Vermehrung der monozytären Zellen, indem die 3 Zellgruppen zusammen 60 % ausmachten. — Die Untersuchung bei der Autopsie von fixierten Koagula aus einer der grossen Venen zeigte, dass das Blut im Todesaugenblicke stark leukaemisch war, und die meisten der Zellen gehörten augenscheinlich der monozytären Reihe an. In den verschiedenen Organen kam typische leukaemische Infiltration mit monozytärem Gewebe vor. Im Knochenmark kam ebenfalls Hyperplasie desselben Gewebes mit starker Verdrängung des normalen Gewebes vor. In den Lymphdrüsen fand sich eine ausgesprochene medullare Reticulose und eine ziemlich ausgesprochene Endotheliose. Dies Krankheitsbild lässt sich schwerlich vollständig erklären. Es ist im höchsten Grade ungewöhnlich, dass eine Leukose mit einer Milzgeschwulst anfängt, die so ausgesprochen ist, dass sie zu einer Zeit, wo keine andere Blutveränderungen als diejenige, die man der Milzhemmung zuschreiben kann, vorhanden sind, eine Splenektomie veranlasst. In diesem Zeitpunkt wird man keine andere Diagnose stellen können als die einer Reticuloendotheliose in der Milz. Der Blutbefund und

die Knochenmarksbiopsie im weiteren Verlauf, verglichen mit dem Resultate der mikroskopischen Untersuchung des Autopsiematerials, stellt jedoch mit Wahrscheinlichkeit fest, dass man wirklich einem Falle von Monozytenleukose gegenübersteht; das periphere Blutbild zeigte aber nach der Röntgenbehandlung streng genommen nichts anderes als Leukozytose mit monozytärer Reaktion mit unreifen Zellen. Inwiefern die Splenektomie eine ursprünglich nicht leukämische Reticulose so beeinflusst hat, dass sie in eine Leukose übergegangen ist, lässt sich natürlich nicht mit Sicherheit feststellen; es liesse sich annehmen, dass man hier einem derjenigen Fälle gegenübersteht, an die Nordenson wahrscheinlich gedacht hat, als er (1939) schrieb: »Eine chronische Reticulose braucht keine peripheren Blutveränderungen inbezug auf das weisse Blutbild zu geben. Durch vermehrte Stimulation entsteht das Bild einer akuten monozytoiden Leukaemie mit tödlichem Verlauf». Endlich liesse sich auch denken, dass man einem Falle von gewöhnlicher Monozytenleukose gegenüberstände, welcher die Abweichung von den gewöhnlichen Fäller zeigte, dass am Anfang eine starke Milzhypertrophie vorhanden war.

Der ***Fall III*** war ein 42-jähriger Mann. Die Erkrankung zeigte einen chronischen, schleichenden Verlauf ohne charakteristische Züge, von einer ständig zunehmenden Anaemie, die extreme Grade erreichte, abgesehen. Die Anaemie war leicht hyperchrom, und da sich bei der Sternalpunktur einzelne typische Megaloblasten fanden, versuchte man (ohne Resultat) eine sehr intense Lebermedikation. Der Tod trat unter dem Bilde einer vorgeschrittenen Anaemie ein. Das Blut zeigte eine stark erhöhte Senkung. Ausserdem fand sich eine zunehmende Leukopenie, wo die Leukozyten normale relative Verteilung und keine pathologische Erscheinungen aufwiesen, abgesehen davon, dass ganz wenige Myelozyten vorkamen und wenige Zellen, die sich morphologisch genau den Monozyten anschlossen, und die den von den beiden anderen Fällen bekannten Promonozyten und Monoblasten glichen. Die Diagnose einer Monozytenleukose wurde erst in Betracht gezogen nach der Untersuchung des Sternalpunktates, worin eine bedeutende Vermehrung der pathologischen Monozyten und ein Teil unreife Zellen vorkamen, welche ganz den Promonozyten und Monoblasten der anderen Fälle glichen. Die Menge dieser Zellen, die bei der ersten Untersuchung zusammen 55.6 % ausmachten, fiel indessen bei der zwei-

ten Untersuchung bis auf 32.6 %. Bei der mikroskopischen Untersuchung des Autopsiematerials fand sich in keinen der Organe etwas Abnormes, spez. keine leukaemischen Veränderungen. Nur im Knochenmark, in der Milz und in den Lymphdrüsen war eine ausgesprochene Reticulose vorhanden, und in der Milz war ausserdem Hyperplasie der Endothelzellen vorhanden. Danach muss die Diagnose Reticuloendotheliose sein. Das interessante bei diesem Fall ist die Tatsache, dass die Knochenmarksbiopsie ein Bild gab, das ganz demjenigen der Monozytenleukose entsprach, und das sich nicht von den übrigen mitgeteilten Fällen unterscheiden liess. Klinisch würde man deshalb zur Diagnose »aleukaemische Monozytenleukose» neigen. Die Autopsie gab indessen wie beschrieben keinen Befund, der die Diagnose einer Leukose berechtigen könnte. Die klinische Diagnose einer »aleukaemischen Leukose» erwies sich also als falsch, da man doch leukaemische Veränderungen in den Organen verlangen muss, um diese Diagnose aufrecht zu erhalten. — Das Bild erinnert an die von Nordenson (1939) mitgeteilten drei Fälle, wo er intravital eine Reticulose diagnostizierte, besonders vielleicht an den einen Fall (Fall 2), wo der Verlauf chronisch war ohne monozytäre Reaktion im peripheren Blute; aber auch nicht bei diesem Falle fand sich bei der Biopsie im Knochenmark bedeutende Vermehrung der monozytären Zellen, sondern nur Zeichen von Reticulose.

## Folgerungen.

Wenn man den Versuch macht, sich auf Grundlage der mitgeteilten Fälle eine Meinung zu bilden über die Lösung einiger der Probleme betreffs des Ursprungs der Monozyten, muss man in Übereinstimmung mit Nordenson feststellen, dass das Resultat recht dürftig ist, da die allgemeinen klinischen und pathologisch-anatomischen Untersuchungen zu grob sind, um exakte Aufschlüsse zu geben. Vieles deutet indessen darauf hin, dass die Monozyten genetisch mit dem reticuloendothelialen System zusammengehören. Beim Falle I, dem klassischen Falle von Monozytenleukose, fand sich in der Milz und in den Lymphdrüsen eine ausgesprochene Reticulose. Beim Falle II deutete der Verlauf der Erkrankung auch im höchsten Grade auf einen engen Zusammenhang zwischen den

beiden Zellsystemen — gleichgültig ob er als eine Monozytenleukose mit etwas atypischem Verlauf oder als eine Reticuloendotheliose mit leukaemoider Reaktion der Monozyten zu deuten ist. Beim Falle III war eine ausgesprochene Reticuloendotheliose in der Milz, in den Lymphdrüsen und im Knochenmark vorhanden; gleichzeitig fand man bei der Knochenmarksbiopsie ein Bild, das der Monozytenleukose so weitgehend ähnelte, dass die Annahme einer nahen Verwandtschaft zwischen der Reticuloendotheliose und der Monozytenleukose berechtigt erscheint. Beim Falle II und III wurde wie erwähnt deutliche Endothelhyperplasie gefunden. Man kann hieraus jedoch nicht folgern, dass die Monozyten von dem Endothel gebildet werden. Über den Ursprung der Monozyten unter normalen Verhältnissen bekommt man keine Aufschlüsse.

*Thaddea & Bakalos* teilten (1939) einen Fall von Monozytenleukose mit, auf Grund dessen sie annehmen, dass die Monozyten aus den Zellen, die im allgemeinen Promyelozyten und Myeloblasten genannt werden, entstehen. Diese Auffassung wird damit begründet, dass die unreifen Zellen, »Monoblasten» und »Promonozyten» morphologisch nicht von den erwähnten Zellen zu unterscheiden sein sollen. Die Verfasser glauben weiterhin Anhaltspunkte dafür zu haben, dass eine Vermehrung der Myeloblasten und Promyelozyten nur bei Fällen, welche klinisch von Monozytose begleitet sind, vorkommen, wohingegen die genannten Zellen nicht von Verhältnissen beeinflusst werden, die auf die granulopoietischen Zellen einwirken, sogar dann nicht, wenn dieser Einfluss weitgehend ist. Stammzellen für die granulierten, segmentkernigen Zellen sollten hiernach die Myelozyten für die Monozyten dagegen die Myeloblasten sein. In dem von mir beschriebenen Falle I fand ich tatsächlich eine starke Ähnlichkeit zwischen Monoblasten und Promonozyten mit jeweils Myeloblasten und Promyelozyten. Wie schon erwähnt fanden sich aber doch Verschiedenheiten in der Kernstruktur, die zwar recht deutlich waren, die aber mit den pathologischen Verhältnissen in Zusammenhang stehen könnten, ebenso wie man bei anderen pathologischen Zuständen gewisse morphologische Veränderungen der Zellen finden kann. Es lässt sich also nicht mit Sicherheit feststellen, dass die von mir beobachteten Monoblasten und Promonozyten mit Myeloblasten und Promyelozyten identisch sind. Die morphologischen Verhältnisse müssen also als unzulänglich angesehen werden, um einen Beweis

oder einen Gegenbeweis für die Auffassung von Thaddea & Bakalos zu liefern, gleichviel ob die morphologischen Verhältnisse Übereinstimmung oder unterschiedliche Befunde ergeben. Weiterhin stimme ich nicht mit den erwähnten Untersuchern in der Auffassung überein, dass die Myeloblasten und Promyelozyten klinisch mit den Monozyten und nicht mit den Myelozyten einen Zusammenhang zeigen. Auf Grund von Erfahrungen mit einem recht grossen Normalmaterial und mit zahlreichen pathologischen Fällen möchte ich vielmehr das Gegenteil annehmen, jedenfalls insofern als zwischen den erwähnten Stammzellen und den Myelozyten ein zweifelloser Zusammenhang besteht. Ich bin der Auffassung, dass man in jedem Präparat von Knochenmarkspunktat deutliche Übergänge zwischen Promyelozyten und Myelozyten findet, da das basophile Protoplasma der Promyelozyten ganz allmählich neutrophil wird, dass man also Zellen beobachten kann, deren Protoplasma z. B. zu drei Vierteln ganz einem Promyelozyten gleicht, während das übrige Viertel eine deutliche beginnende neutrophile Reaktion zeigt. Ebenso kann man (vielleicht vorwiegend in pathologischen Fällen mit Eosinophilie) deutliche Eosinophilie in einem sonst schönen Promyelozyten finden. Meine Beobachtungen können also nicht widerlegen, dass die Monozyten aus den Promyelozyten entstehen könnten, hingegen sprechen sie gegen die andere Beobachtung Thaddea & Bakalos's, dass nämlich die Promyelozyten unter normalen und pathologischen Verhältnissen nicht mit der Granulopoiese im Zusammenhang stehen. Meine Beobachtungen stimmen mit Sabin, Austrian, Cunningham & Doan überein, die in einem Falle von Myeloblastenleukose deutliche Beziehungen zwischen Myeloblasten und Myelozyten gefunden haben.

Betreffs der Frage Monozyten-Histiozyten geben die von mir untersuchten Fälle keine Aufschlüsse, da ich leider in dem Zeitpunkt, wo die Beobachtungen gemacht wurden, nicht im Stande war, festzustellen, ob die von mir gefundenen Zellen zu der einen oder der anderen Gruppe gehörten, was nur durch Supravitalfärbung konstatiert werden kann.

Die Frage, ob aleukaemische Monozytenleukose eksistiert oder nicht, lässt sich auch nicht durch meine Beobachtungen aufklären. Der Fall III war solcher Art, dass man die erwähnte Diagnose intravital auf Grundlage der Befunde bei der Knochenmarksbiopsie stellte. Das Autopsieresultat hat zweifellos die Diagnose umge-

stossen. Ob sie eksistiert oder nicht, weiss ich nicht, aber es scheint, als ob man, um diese Diagnose aufrecht zu erhalten, ein typisch leukaemisches Bild bei der postmortalen Mikroskopie der Organe verlangen muss. Findet man dieses Bild nicht, muss man sich mit der Diagnose einer Reticulose begnügen. Einer der Pioniere der »aleukaemische Reticulose», Dameshek, schreibt (1933), dass die aleukaemische Reticulose sich zur Monozytenleukose verhält wie aleukaemisch lymphatische und aleukaemisch myeloide Leukose zu lymphatischer beziehungsweise myeloider Leukose. Dieser Vergleich dürfte kaum haltbar sein, da die neueren Untersuchungen ziemlich sicher darauf deuten, dass nicht jede Reticulose eine Monozytenleukose bedeutet. Man kann also nicht die Bezeichnung Reticulose als synonym mit Monozytenleukose gebrauchen, da die Monozytenleukose eine Unterabteilung des Gesamtbegriffes Reticulose ist; dies schliesst aber die Möglichkeit des Vorkommens einer aleukaemischen Monozytenleukose nicht aus.

## Resumé.

Es wurden drei Fälle von Reticulose mitgeteilt. Der eine Fall war eine typische Monozytenleukose; der andere Fall war wahrscheinlich eine atypische Monozytenleukose. Der dritte Fall zeichnete sich dadurch aus, dass bei der Knochenmarksbiopsie ein Bild gefunden wurde, das der Monozytenleukose glich, während gleichzeitig das Blut keine entsprechenden Veränderungen aufwies. Die Diagnose einer aleukaemischen Monozytenleukose wurde intravital gestellt, die Autopsie indessen zeigte, dass diese Diagnose der Diagnose einer Reticulose weichen musste, da in den Organen keine leukaemischen Veränderungen vorkamen. Das Verhältnis der Monozyten zu dem reticuloendothelialen System wird auf dieser Grundlage besprochen. Unter pathologischen Verhältnissen stehen die Monozyten wahrscheinlich zu dem reticuloendothelialen System in nahem genetischem Verhältnis.

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# On the Site of Production of Pathologically Increased Globulin as Elucidated by Conditions in Cerebro-spinal Fluid.

By

JENS BING and AXEL V. NEEL.

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The problem of where albumin and globulin are formed in the blood and the serous cavities has been the subject of much research, but up to the present no one knows where these proteins are formed in the normal organism. On the other hand, recent years have seen the publication of works showing that one feature common to diseases involving hyperglobulinaemia is that there is an accumulation of plasma cells and other reticuloendothelial cells in the morbid tissues. This fact, first demonstrated by Bing and Plum (2) and afterwards affirmed by many other authors (5, 6, 8, 9, 14, 15, 1), gave rise to the opinion that serum globulin is formed in these cells. This theory of the genesis of globulin was recently supported by the work of Bjørneboe and Gormsen (4), who showed that when rabbits are immunised with pneumococci of various types, the results include both pronounced hyperglobulinaemia and a marked increase in the number of plasma cells, especially in the spleen but also in the liver, kidneys and lymphatics.

The following communication contains an account of the various changes observed in the globulin content of the spinal fluid in affections of the central nervous system and its sheaths; as in the

reports on hyperglobulinaemia research, a comparison will be made between the protein values found and the histological changes in the affected tissues.

Whereas conditions *in serum* — as regards the manner in which globulin is pathologically increased — are less easily visualized owing to the high protein content in serum and the many different tissues through which the blood passes, matters are much clearer when one is occupied with the globulin increase in the cerebrospinal fluid, which is encased in the cerebral and spinal membranes, in which normally there is only a very low protein content. Almost from the time when the lumbar puncture came into wide use it has been known that increased globulin occurs with chronic inflammation, particularly in cases of dementia paralytica. The significance of this globulin increase was considered to be so great that many workers, especially in the germanic countries, almost until quite recently concentrated on it alone when determining the protein content in the cerebrospinal fluid; their method was to carry out the Nonne-Apelt-Schumm reaction by mixing equal parts of the fluid and saturated neutral $Am_2\ SO_4$ solution and then measure the strength of the precipitate of globulins. Already before that time Guillain in France had devised a similar reaction with magnesiumsulphate.

When making both a globulin determination and a total-protein determination by employing, as in Denmark, the respective methods of Ross-Jones-Bisgaard and Roberts-Stolnikow-Brandberg- Bisgaard-Zalociecki for ascertaining the weakest concentration at which precipitation occurs at the junction between a cerebrospinal fluid or diluted cerebrospinal fluid above, and below a saturated neutral $AM_2SO_4$ solution ($Am_2SO_4$ value=»globulin») or respectively a ca 28 % $HNO_3$ solution ($HNO_3$ value=total-protein), it was found that in very pronounced cases of dementia paralytica there might be cerebrospinal fluids in which the pathological protein increase consisted almost exclusively of globulins. — In contrast, in the case of acute purulent meningitis there was a relatively slight globulin increase in proportion to a very considerable increase of the total-protein content, or, in other words, a large increase of the albumin content. Accordingly, the preponderating globulin increase must have been caused by the chronic inflammation, the albumin increase by the acute inflammation.

The introduction of colloidal reactions (goldsol, mastix etc.) led to the finding of various curves of precipitation, i. e. »the paralytic curve» where the precipitation was found to occur in the first tubes in the dilution series, and »the meningitic curve» where precipitation occurred in the later tubes in the series. As was shown by one of us in 1915 (10), the various curves were due mainly to the relation between globulins and albumins in the cerebrospinal fluid, there being precipitation in the first tubes, where there was preponderantly a globulin increase as in Dementia paralytica, but also e. g. in certain cases of multiple sclerosis with a similar globulin increase in the cerebrospinal fluid, whereas the precipitation resulted later in the dilution series when, as with acute purulent meningitis, there was a relatively slight globulin increase in proportion to the albumin increase. In other words, the globulins precipitate the colloidal solution whereas albumins are protective against precipitation.

Investigations into the goldsol reaction to serum dilutions and comparisons between this reaction and the Wassermann reaction revealed (11) that with self-inhibitory sera and with Wassermann-positive sera there was a considerable globulin increase in these sera, for, in contrast to normal sera, they gave a goldsol reaction of a form similar to that in Dementia paralytica. When determining the protein content by Bisgaard's method with self-inhibitory sera a dilution of e. g. 1/50 gave a globulin value of 8 as against a total-protein figure of 30, whereas proportions like 4—60 were found in normal serum. — These selfinhibitory sera came mostly from patients with »myelomata» [Jersild (7)]. Subsequent investigations have shown that in these cases the growths are usually plasmocytomata. In this connection more interest is attached to the demonstration of the change in the globulin content in Wassermann-positive sera found in the course of anti-syphilitic treatment, while simultaneously the Wassermann reaction gradually changed from strongly positive to negative.

In three cases of fresh syphilis the following values were found — the first figure representing the globulin value, the second the total-protein in a serum dilution of 1/50 (12).

| | | |
|---|---|---|
| I 23/2 19 9—30 | II 28/2 10—25 | III 20/3 10—30 |
| 10/3 19 7—30 | 10/3 5—30 | 10/4 7—30 |
| 23/3 19 5—40 | 8/4 5—30—35 | 26/4 6—30 |

In analogy with conditions in cerebrospinal fluid, where chronic inflammatory changes in the central nervous system are able to produce a globulin increase in the fluid, one would assume that the chronic inflammatory changes, which experience shows take place in syphilis in the organism outside of the central nervous system, had succeeded in affecting and in-

creasing the globulin content in serum; this assumption was further confirmed by the fact that this globulin increase declined at the same time as the anti-syphilitic treatment caused the inflammation to recede or to disappear. — The same thing is seen, but more clearly, in regard to the cerebrospinal fluid, for there the protein increase declines gradually as the inflammatory changes in the central nervous system recede either spontaneously or as the result of treatment.

Naturally it is not the intention here to examine *the normal protein content in cerebrospinal fluid;* reference may be made to textbooks and earlier works (10, 13). Normally we find from 13 to 28 mg % protein in cerebrospinal fluid, and of this about 1/5th is globulin. Normally the space containing the cerebrospinal fluid is a closed system separated from the circulatory system by a barrier between blood and fluid and between blood and central nervous system. This barrier is impermeable to colloids, but permeable to crystalloids. Under pathological conditions, especially in the case of inflammatory processes in the brain and its membranes, these conditions change, but the changes in the cerebrospinal fluid are very preponderantly a product of the changes in the central nervous system and its meninges.

On the other hand, it is not all cases of protein changes in the cerebrospinal fluid that are of interest in this connection. We must leave out all those cases where the protein increase wholly or partly is due to the results of pressure with venous stasis and a consequent permeation of protein from the blood vessels. Under such conditions protein increase is to be found in cases of cerebral tumour, obstruction in the spinal canal as a consequence of tumours in and near the spinal cord, in localised arachnoiditis with obstruction, tubercular spondylitis or metastases to the spinal column with compression, in polyradiculitis, etc. A feature common to these lesions is a considerable increase of protein of a composition corresponding almost to that of the blood and with little or no cell increase. Protein increases as a result of haemorrhage must also be excluded, as our sole interest in this work is protein increase owing to inflammation.

Of *inflammatory processes* we must first rule out those in which the course is short, because the patient either dies or recovers so that there is no time for the development of protein changes to any great extent. This applies to the benignant forms of *lymphocytic meningitis* and *poliomyelitis.* In the latter disease, where primarily

there are polynuclear cells in the cerebrospinal fluid, later mostly lymphocytes and occasional reticulo-endothelial cells, and a very low albumin content in proportion to the number of cells, it sometimes happens in a later stage, when clinically there is pronounced paresis, that one finds a fairly considerable increase of protein and a proportionately slight increase of cells. In our opinion, however, the increased protein here is due to radiculitis with compression, as mentioned above.

In *acute purulent meningitis* we find in the cerebrospinal fluid a polynuclear (polymorphonuclear) formula and a considerable protein increase. As a rule the cell count is very high (1,000—20,000 cells per $mm^3$ or more), and generally the fluid macroscopically is more or less turbid and sometimes very purulent. The protein content is also very high, but the globulin content is relatively low in proportion to the total-protein content — in other words, in all essentials an increase of albumin. We find globulin-total-protein values like 6—160; 10—250; 6—150 (10, p. 109). Pathologically in the acute stage we find leptomeninges (pia-arachnoidea) much thickened and with a considerable infiltration of polymorphonuclear leucocytes. If the disease is cured in the acute stage by means of chemo-therapeutics, the cell and protein contents in the cerebrospinal fluid return gradually to the normal. If the disease becomes more chronic, conditions change in both meninges and cerebrospinal fluid, and we find partly polymorphonuclear leucocytes, partly mononuclear cells, lymphocytes, plasma cells and reticulo-endothelial cells. In the cerebrospinal fluid we find a similar cell formula, and the globulin value rises in proportion to the albumin content, so that we see dilution figures such as 5—70, 3—50, 1—25 (l. c. p. 109).

A somewhat similar protein content is to be found in *tuberculous meningitis*, where the course is more chronic in character and where the cells in the cerebrospinal fluid consist mainly of lymphocytes and large mononuclear cells. In certain instances there are some polymorphonuclear cells. The dilution values found are such as 3—50, 1—15, 10—200, 4—60. 3—40 (l. c. p. 109). In some forms of meningitis there may sometimes be very high values, e. g. 25—550 in tuberculous meningitis; in these cases, however, it is presumable that a certain role is played by compression caused by thickened and infiltrated meninges at foramen magnum.

In tuberculous meningitis, which almost always is associated with miliary tuberculosis, we find that in addition to the specific tuberculous changes (the miliary tubercles, with whose structure the reader is assumed to be familiar), there is also an infiltration of lymphocytes, large mononuclear cells and reticulo-endothelial cells. Plasma cells in larger or smaller numbers are a regular feature.

In *cerebrospinal syphilis* the cerebrospinal fluid is found to be the seat of a more or less pronounced cell increase, consisting of lymphocytes and a few large mononuclear cells, and it also has a protein content with dilution values similar to those in tuberculous meningitis (5—60, 5—70, 10—250, 5—30). In the meninges and along the vessels running from pia down into the brain there is infiltration consisting mainly of lymphocytes, in which are a few plasma cells. There are also proliferation of the reticulo-endothelial tissue and vascular changes more specific in nature (Heubner's endarteritis). If this process can be cured by treatment, both the cell and the protein changes in the cerebrospinal fluid will disappear at the same time; in such cases it is possible to find completely normal conditions in the fluid, even according to the strictest standards. — On the other hand, in latent syphilis one often finds quite slight changes in the cerebrospinal fluid, for example cells 3—5/3 globulin 0 (1 ?), total-protein 8—10, as the expressions of a discrete syphilitic inflammation which as a rule is unimportant and in itself does not call for any treatment.

However, the most pronounced globulin increase in the cerebrospinal fluid is regularly found in untreated cases of *dementia paralytica*. Here we have dilution values such as 4—15, 3—15, 7—25, 8—30 etc. (l. c. p. 109). Bisgaard (l. c. pp. 39—41) found still greater globulin increases like 20—35, 20—45. Precipitation with semi-saturated $(NH_4)\ SO_4$ in these cases shows that the protein increase is due to globulin almost exclusively, whereas the albumin fraction is only very slightly increased. The inflammatory changes in dementia paralytica, which alone have a bearing on the changes in the cerebrospinal fluid, are localised to the leptomeninges and to the cerebral cortex, especially in the frontal regions and in certain parts of the central ganglia, particularly in corpus striatum. In both leptomeninges and cerebral cortex the infiltration consists chiefly of plasma cells, which in the cortex lie partly around the larger vessels together with lymphocytes, but mainly lie in the

form of a dense coating around the precapillaries and capillaries, as well as freely in the tissues here and there. — The plasma cells may be so dense that they form a kind of paving around the vessels, their shape being affected by this close massing. In the cortex they are therefore usually oblong, angular, whereas in pia, where they lie more loosely, they are round.

As far as the cells are concerned (lymphocytes and some plasma cells) the changes in the cerebrospinal fluid are caused by the infiltration in the leptomeninges; but not uncommonly this infiltration is so sparse that there are only very few cells in the cerebrospinal fluid, even if there is a typical, well-marked globulin increase and a strongly positive Wassermann reaction. In such cases these changes must therefore emanate mainly from inflammatory changes in the brain itself. After a successful malaria treatment we now find that the changes in the cerebrospinal fluid recede very considerably, and it is possible to find almost normal — indeed, in the opinion of many authors, completely normal — cell and protein values in the fluid, e. g. cells 3/3, globulin 0 (1 ?), total-protein 10—11. At the same time the Wassermann reaction is negative. When the central nervous system of patients who have died at this stage is examined, we find only very slight and sporadic inflammatory changes with a few plasma cells and lymphocytes here and there; indeed in many cases they are found only after careful searching.

In the case of another lesion of the central nervous system, viz. *multiple sclerosis*, it is often possible in the acute stage or during a recrudescence of the process in the chronic stages to find changes in the cerebrospinal fluid which, as regards cell and protein contents (globulin preponderance), are quite like those observed in dementia paralytica. In such cases we also find a »paretic», first zone by means of the goldsol reaction, but of course no positive Wassermann reaction. Pathologically there are widespread inflammatory changes, not only in and about the fresh sclerotic plaques, but also in the cerebral tissue itself, especially in the white matter near the ventricles. The infiltration consists of lymphocytes and plasma cells in varying proportions. Similar infiltrations are to be found in the leptomeninges, to a greater or smaller extent. The very fact that such changes are present argues strongly that in typical multiple sclerosis we have to do with an infectious disease. — These inflammatory changes recede in most cases, and examination of chronic

cases, even with very pronounced clinical symptoms, usually reveals no sign of inflammation in the sclerotic plaques. There are only very slight changes in the cerebrospinal fluid in these cases, and many authors indeed regard it as being quite normal. This means that the sclerotic changes in the central nervous system itself cause no protein changes in the cerebrospinal fluid, these changes having receded and disappeared together with the inflammatory changes.

## Conclusions.

As a result of a comparison of the protein content in the cerebrospinal fluid and the cellular reaction accompanying the various affections of the central nervous system, it is found that an increased globulin content unaccompanied by a corresponding albumin increase occurs only in diseases which pathologically are characterized by accumulation of plasma cells. This finding agrees with the fact that in hyperglobulinaemia there is an accumulation of plasma cells and other reticulo-endothelial cells in the organism. Consequently there is reason for assuming that these cells form the globulin of both blood and cerebrospinal fluid. In a number of cases a massing of lymphocytes is observed besides the plasma cells. Nevertheless the lymphocytes must not be assumed to play any role in the formation of globulin, because no hyperglobulinaemia is to be found when there is an isolated increase of lymphocytes such as is observed e. g. in lymphadenoses, whereas an isolated increase of plasma cells, for example in myelomatosis, gives a considerable globulin increase.

## Summary.

It is found to be a feature common to those diseases which present isolated globulin increase in the spinal fluid that there is an accumulation of plasma cells in the central nervous system and its meninges. This agrees with the fact that in all the various diseases with hyperglobulinaemia there is accumulation of plasma cells and other reticulo-endothelial cells and suggests that it is these cells that form the globulin.

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48975

# Heparin and the blood sedimentation reaction.

By

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(Submitted for publication February 20th, 1942).

During the last few years several works have been published — especially from Swedish quarters — which deal with the sedimentation reaction carried out with heparin as anticoagulant. In 1936 Enocksson and his collaborators treat the heparin sedimentation reaction as compared with Westergren's citrate method. They employ Westergren's stand, but stabilize the blood by damping the syringe with $^1/_{15}$—$^1/_{20}$ $cm^3$ of a 1 per cent heparin solution. Their experiments show that with the blood from normal people rather a constant conformity is obtained between the heparin sedimentation reaction carried out in this way and the citrate sedimentation reaction, while by pathological sedimentation reactions no conformity at all can be demonstrated. Enocksson and his collaborators regard the heparin sedimentation reaction as the »natural» sedimentation reaction contrary to the citrate sedimentation reaction, heparin being the own anticoagulant of the organism. The fact that by pathological sedimentation reactions hardly ever higher sedimentation values are obtained with heparin blood than with citrate blood, in their opinion is due to the greater »sensitiveness» of the heparin.

In 1937 Westergren stated that his experiments have clearly shown that the heparin sedimentation reaction gives great deviations and that, at any rate, it has no advantages. In 1938 Wilander

finds that the sedimentation reaction carried out with heparin blood in the usual way according to Westergren's method (one part 3.8 per cent Na.-citrate plus four parts heparin blood) gives the same results as carried out with citrate blood without addition of heparin. Magnussen and Justus Strøm have found — independently of each other — that the heparin sedimentation reaction as hitherto carried out gives great deviations as compared with the citrate sedimentation reaction. Thus Justus Strøm finds that the results of experiments with citrate blood sedimentations, pure heparin blood sedimentations and heparin-citrate blood sedimentations are in the proportion of 1 to 3.2 to 1.2. His experiments further show that both by normal and moderately increased sedimentation reaction heparin sedimentation reactions carried out at the same time show considerably higher values. On the other hand, he not seldom finds blood samples giving a high citrate sedimentation reaction, but which stabilized with heparin give considerably lower sedimentation values. Moreover, Justus Strøm finds contrary to Wilander that heparin-citrate sedimentation reactions give higher values than corresponding citrate sedimentation reactions. From this he draws the conclusion — as the heparin must have changed the stability of the erythrocytes — that the heparin sedimentation reaction — like the citrate sedimentation reaction — is an »artificial product» and not as formerly maintained a »natural» sedimentation reaction.

In 1939 v. Kaulla has investigated whether the sedimentation reaction carried out with citrate-blood differs from the sedimentation reaction carried out with pure heparin blood, and the defects connected with this heparin sedimentation method. He employs Westergren's stand in such a manner that the addition of fluid by all tests with heparin blood is 8 per cent. He varies the heparin concentration from 0.02 mg to 4 mg per $cm^3$ blood. The experiments show: 1) that by experiments with normal blood the sedimentation rate increases with increasing heparin concentration, and 2) that double tests with heparin-stabilized blood often give results greatly deviating from each other, and finally 3) that by high sedimentation reactions often lower values are obtained with heparin blood than with citrate blood.

When attempting to use capillary blood stabilized with heparin for a micro sedimentation reaction the author found it expedient first to examine if it was possible with a heparin macro sedimenta-

tion method to obtain the same sedimentation values as with Westergren's citrate sedimentation method. A series of blood sedimentation experiments was therefore carried out, partly with non-diluted heparin blood, partly with blood, to which was added heparin in solution. When diluted heparin blood was used, the dilution was in all cases as by Westergren's method: 1 part stabilization fluid to 4 parts blood.

*1.* Experiments with non-diluted heparin blood.

By non-diluted heparin blood in this connection is understood blood taken in a syringe damped with a heparin solution. The experiments confirmed that the rate of sedimentation of the blood corpuscles increased with increasing heparin concentration, and that double tests gave very deviating results.

*2.* Experiments with blood stabilized with heparin dissolved in distilled water.

In these experiments hemolysis was ascertained in the heparin samples, which made this method of dissolution inavailable.

*3.* Experiments with blood stabilized with heparin dissolved in sodium chloride solution.

First a series of experiments was carried out, in which the concentration of heparin was varied from 1 per cent to 0.1 per thousand. A heparin concentration of 1 per thousand was found most suitable for the following experiments.

Next further particulars of a series of experiments shall be mentioned, in which the sedimentation reaction was executed partly in the usual way with citrate blood, partly with blood, the coagulation of which was prevented by addition of a heparin-sodium chloride solution. The heparin concentration was in all these experiments 1 per thousand, while the sodium chloride concentrations were 0.3—0.5—0.7—0.9 and 1.5 per cent. Double tests both of citrate blood and of heparin blood were arranged and after 1 hour the reading off took place. The figures I—V are graphic representations of the results of these experiments. The ordinate of each of the points states the average values of the figures for the double tests with citrate blood, while the abscissa of the points shows the corresponding figures for the double tests with heparin blood.

The experiments with 0.3 per cent sodium chloride solution as dilution fluid (figure I) show that the results of the heparin blood sedimentation reactions by this salt concentration are lower than

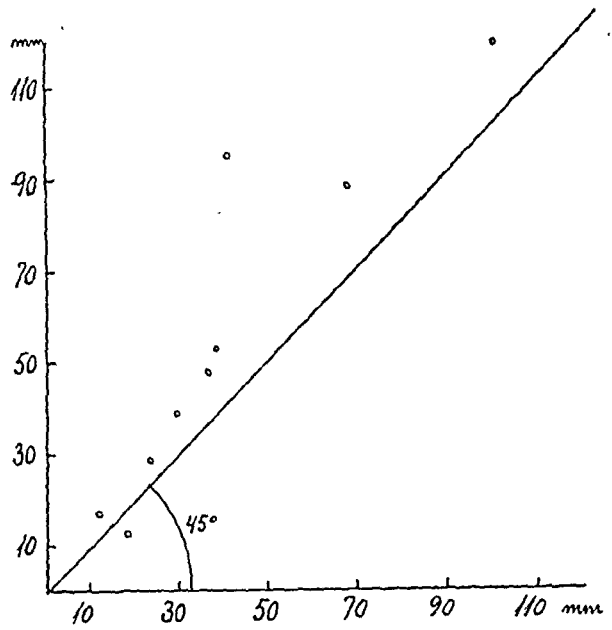



*Figure I.*

*Ordinate:* The average values of the figures for double tests with citrate blood.
*Abscissa:* The average values of the figures for double tests with blood stabilized with 1 per thousand heparin in 0.3 per cent sodium chloride solution.

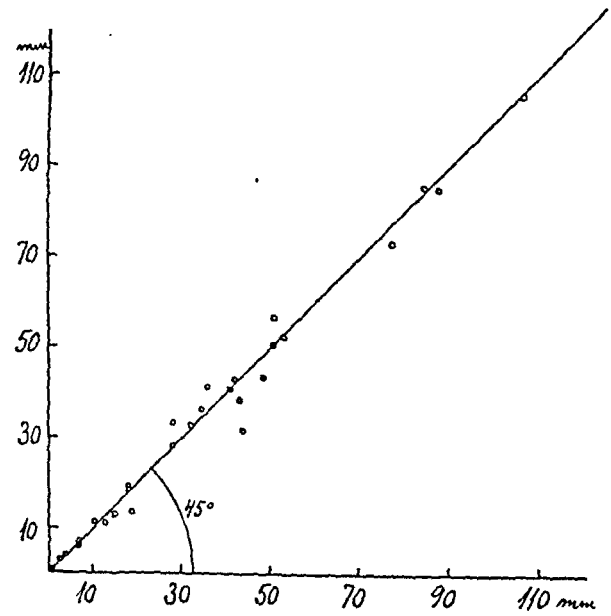



*Figure II.*

*Ordinate:* The average values of the figures for double tests with citrate blood.
*Abscissa:* The average values of the figures for double tests with blood stabilized with 1 per thousand heparin in 0.5 per cent sodium chloride solution.

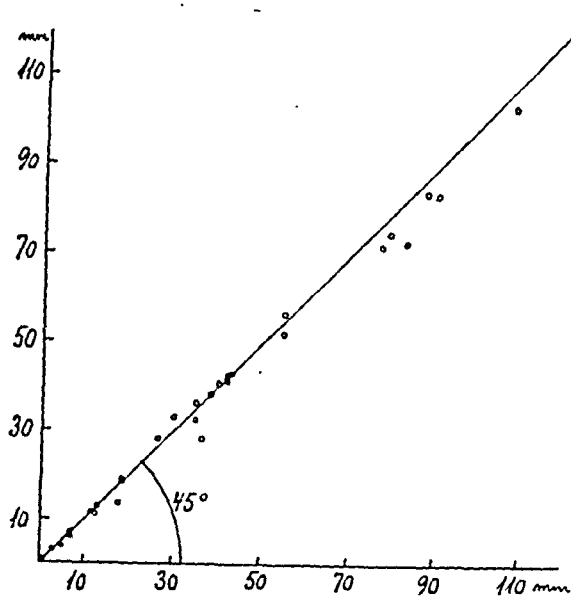



*Figure III.*

*Ordinate:* The average values of the figures for double tests with citrate blood.
*Abscissa:* The average values of the figures for double tests with blood stabilized with 1 per thousand heparin in 0.7 per cent sodium chloride solution.

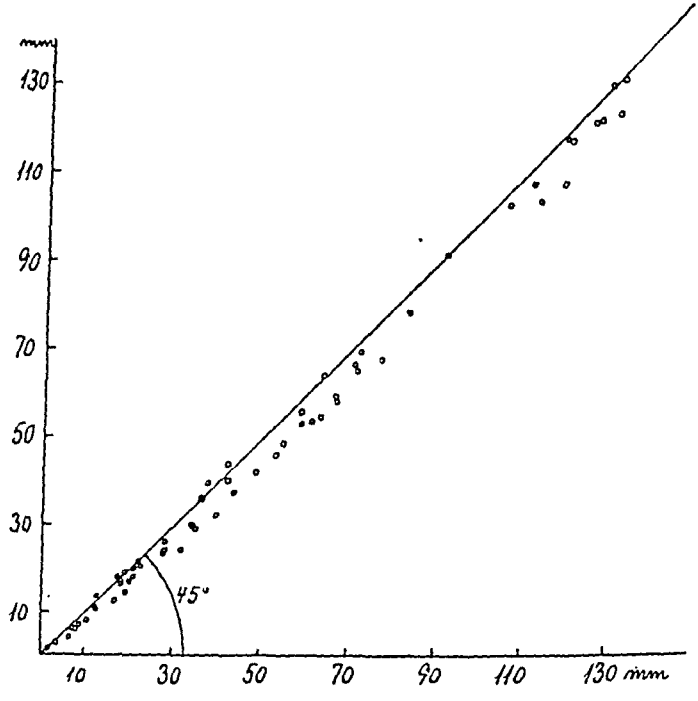



*Figure IV.*

*Ordinate:* The average values of the figures for double tests with citrate blood.
*Abscissa:* The average values of the figures for double tests with blood stabilized with 1 per thousand heparin in 0.9 per cent sodium chloride solution.

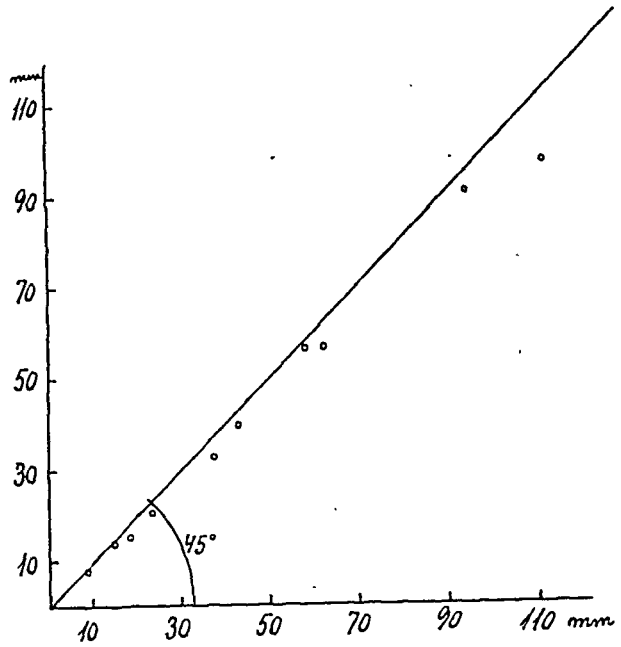



*Figure V.*

*Ordinate:* The average values of the figures for double tests with citrate blood.
*Abscissa:* The average values of the figures for double tests with blood stabilized with 1 per thousand heparin in 1.5 per cent sodium chloride solution.

the values for the citrate blood sedimentations reactions. Besides, there was some hemolysis in the tubes with heparin blood.

With a heparin solution containing 0.5 per cent sodium chloride as stabilization and dilution fluid (figure II) the experiments show that with the heparin blood samples sedimentation values are obtained which are identical with the results of the corresponding citrate blood sedimentation reactions. As expected, there was no hemolysis in the sedimentation tubes with heparin blood.

Diluted with 0.7 per cent sodium chloride solution heparin sedimentation reactions (figure III) with values up to abt. 60 mm/1 hour likewise show identity with the controls with citrate blood, while the heparin tests with sedimentation values beyond this limit generally are a few mm higher than the citrate tests.

In figure IV are recorded the results of 61 sedimentation experiments, in which partly citrate blood, partly blood diluted with a heparin solution containing 0.9 per cent sodium chloride was used. As the figure shows, the sedimentation values in their entirety were somewhat higher than the corresponding values for the citrate sedimentation reactions.

**Table 1.**

*The difference between double tests on the same blood sample.*

| 3.8 per cent Na-Citrate double tests mm/1 hour | Difference in per cent of the average | 1 per thousand heparin in 0.9 per cent NaCl Double tests mm/1 hour | Difference in per cent of the average. |
|---|---|---|---|
| 1.5— 1.5 | 0 | 1.5— 2.0 | 28.5 |
| 3.0— 3.0 | 0 | 3.5— 4.0 | 13.3 |
| 4.0— 4.5 | 11.7 | 6.0— 7.0 | 15.3 |
| 5.5— 6.5 | 16.6 | 6.5— 7.5 | 14.2 |
| 6.0— 6.0 | 0 | 8.0— 8.0 | 0 |
| 7.0— 7.0 | 0 | 9.0— 9.0 | 0 |
| 8.0— 8.0 | 0 | 10.0—11.0 | 9.5 |
| 8.5— 9.0 | 5.7 | 10.0—10.0 | 0 |
| 10.0—11.0 | 9.5 | 12.0—13.0 | 8.0 |
| 10.5—11.5 | 9.0 | 11.5—13.0 | 12.2 |
| 12.0—13.0 | 8.0 | 17.0—17.0 | 0 |
| 12.0—15.0 | 22.2 | 12.0—13.0 | 8.0 |
| 14.0—15.0 | 6.8 | 19.0—19.5 | 2.5 |
| 16.0—17.0 | 6.0 | 18.0—18.0 | 0 |
| 17.0—17.0 | 0 | 20.0—20.0 | 0 |
| 17.0—17.0 | 0 | 17.5—19.0 | 8.2 |
| 17.0—19.0 | 11.1 | 17.0—18.0 | 5.7 |
| 18.0—18.0 | 0 | 21.0—21.0 | 0 |
| 19.0—19.0 | 0 | 19.0—19.0 | 0 |
| 19.0—21.0 | 10.0 | 20.0—22.0 | 9.5 |
| 20.0—21.0 | 4.8 | 22.0—23.0 | 4.4 |
| 21.0—22.0 | 4.6 | 21.0—23.0 | 9.0 |
| 22.5—24.0 | 6.4 | 27.0—28.0 | 3.6 |
| 24.0—24.0 | 0 | 27.0—29.0 | 7.1 |
| 24.0—25.5 | 6.0 | 31.0—32.5 | 4.7 |
| 25.0—27.0 | 7.6 | 28.0—28.0 | 0 |
| 28.0—30.0 | 6.8 | 35.0—35.0 | 0 |
| 29.0—31.0 | 6.6 | 33.0—35.0 | 5.8 |
| 32.0—32.0 | 0 | 39.0—40.0 | 2.5 |
| 36.0—36.0 | 0 | 36.0—36.0 | 0 |
| 37.0—38.0 | 2.6 | 42.0—45.0 | 6.8 |
| 40.0—40.0 | 0 | 40.0—44.0 | 9.5 |
| 40.0—39.0 | 2.5 | 37.0—38.0 | 2.6 |
| 41.0—47.0 | 13.6 | 41.0—43.0 | 4.7 |
| 42.0—42.0 | 0 | 48.0—49.0 | 2.0 |
| 45.0—47.0 | 4.3 | 53.0—53.0 | 0 |
| 48.0—49.0 | 2.0 | 54.0—55.0 | 1.8 |
| 53.0—53.0 | 0 | 58.0—59.0 | 1.7 |
| 53.0—54.0 | 1.8 | 60.0—61.0 | 1.6 |

Table 1. Concl.

| 3.8 per cent Na-Citrate double tests mm/1 hour | Difference in per cent of the average | 1 per thousand heparin in 0.9 per cent NACl Double tests mm/1 hour | Difference in per cent of the average |
|---|---|---|---|
| 53.0—56.0 | 5.5 | 63.0—63.0 | 0 |
| 56.0—56.0 | 0 | 58.0—59.0 | 1.7 |
| 57.0—59.0 | 3.4 | 63.0—70.0 | 10.5 |
| 59.0—60.0 | 1.6 | 66.0—67.0 | 1.5 |
| 63.0—65.0 | 3.0 | 63.0—64.0 | 1.5 |
| 65.0— 65.0 | 0 | 70.0— 72.0 | 2.8 |
| 65.0— 70.0 | 7.4 | 74.0— 80.0 | 7.7 |
| 66.0— 67.0 | 1.5 | 70.0— 71.0 | 1.4 |
| 69.0— 70.0 | 1.4 | 72.0— 72.0 | 0 |
| 77.0— 80.0 | 3.8 | 82.0— 84.0 | 2.4 |
| 91.0— 92.0 | 1.0 | 91.0— 92.0 | 1.0 |
| 101.0—105.0 | 3.8 | 105.0—107.0 | 1.8 |
| 103.0—105.0 | 1.9 | 112.0—114.0 | 1.7 |
| 104.0—112.0 | 7.4 | 117.0—121.0 | 3.3 |
| 107.0—109.0 | 1.8 | 111.0—112.0 | 0.8 |
| 117.0—119.0 | 1.6 | 120.0—121.0 | 0.8 |
| 117.0—120.0 | 2.5 | 119.0—120.0 | 0.8 |
| 120.0—124.0 | 3.2 | 126.0—126.0 | 0 |
| 120.0—125.0 | 4.0 | 126.0—129.0 | 2.3 |
| 122.0—126.0 | 3.2 | 130.0—134.0 | 3.0 |
| 129.0—132.0 | 2.2 | 129.0—131.0 | 1.5 |
| 131.0—133.0 | 1.5 | 132.0—134.0 | 1.5 |

There was no difference worth mentioning between the results in experiments with 0.9 per cent and 1.5 per cent sodium chloride solution (figure V).

In order to examine more closely the non-casual deviations table 1 has been made, in which the results of the above-mentioned 61 experiments have been stated according to the size of the sedimentation reactions. The experiments have been carried out as double tests with citrate blood and heparin blood, where the heparin concentration was 1 per thousand in 0.9 per cent sodium chloride solution. The experiments have been carried out on blood from patients partly from the medical-epidemic department, by preference from patients with acute infectious diseases, partly from patients from the dermatological-venerological department. In column 1 you find the results of the sedimentation reactions with citrate

blood, and in column II the difference between the double tests in per cent of the average value is stated. In column III and IV you find the corresponding figures for the heparin blood tests. Apart from sedimentation reactions with values up to 10 mm, where the reading deviation of 0.5 mm percentually plays an incomparably great part, you will find as far as the other reactions are concerned that the unsystematic variation is the same for the two methods.

As appears from the above, it is possible to carry out the blood sedimentation reaction with heparin as anticoagulant and still obtain the same results as with Westergren's method, if the following 3 conditions are met with:

1) the heparin concentration must be 1 per thousand.

2) the blood must be diluted in the same proportion as by Westergren's method.

3) the dilution fluid must contain a certain salt concentration (as far as the sodium chloride is concerned 0.5—0.7 per cent.)

## Summary.

A method of determining the sedimentation reaction carried out with heparin blood is indicated.

The experiments show that in order to obtain the same results as by Westergren's method a certain heparin concentration and a dilution of the blood (in the same proportion as by Westergren's method) with a salt solution of a certain concentration are necessary.

Of 61 experiments with double tests both of citrate blood and of heparin blood appears that the exactitude of the two methods is the same.

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# Experimental studies on production of pernicious anemia by operation on the digestive tract.[1]

## 4. Results of Extensive Resection of the Distal Part of the Small Intestine (on Pups).

By

SVEND PETRI, HANS JENSENIUS, FLEMMING NØRGAARD & ERIK THYSSEN.

(Submitted for publication December 5th, 1941).

## Introduction:

As a part in our systematic experiments on production of pernicious anemia by single or combined resections of anatomically definable regions in the stomach, duodenum and small intestine, the last ones were made with resection of the pylorus + the Brunner-gland section of the duodenum + the distal $^2/_3$ of the small intestine (Petri, Jensenius & Thyssen, 1941). Also this type of operation failed to result in typical pernicious anemia, but it constantly produced a pellagrous symptom complex. For the first time, moreover, the clinical picture of these dogs presented also a special feature (tendency to hyperchromic, macrocytic anemia and chronic diarrhea) presumably ascribable to the resection of the small intestine. For elucidation of the causal significance of the resection of the small intestine to the appearance of the pellagrous symptoms and especially the above-mentioned particular features, the resections reported in the following were carried out.

[1] These studies have been carried out with the aid of a grant from P. Carl Petersen's fond and private means.
Translation from Danish by Hans Andersen, M. D.

## Previous Investigations.

If in this connection we leave out the experimental extirpation of the duodenum (Mann & Kavamura, 1922; Hauswirth & Silberstein, 1928, 1931; and Aron & Bauer, 1933). Experimental resection of the small intestine, together with systematic examination of the blood, has been reported only in a few, scattered cases in which the clinical data were scanty.

Bence (1936) thus removed 3 m of *ileum and jejunum* on a swine, 3 months old. The observation period was 9 months. No anemia was observed, but there was a rise in the hemoglobin percentage and red blood count (*i. e.*, normo-hypochromic polycytemia).

Brown (1938) resected almost the entire small intestine, or a large part of it, on 3 swine. The length of the observation period is not given. No anemia or diarrhea was observed.

Miller & Rhoads (1935) state that the blood picture in dogs after resection of nearly the entire ileum showed merely a slight hypochromic anemia.

## Material and Experimental Conditions.

The present experiments were carried out on 3 pups, 5 months old, namely: No. 121, female, weighing 5.7 kg, and measuring 53 cm; No. 105, male, 6.6 kg, 48 cm; and No. 118, male, 7,8 kg, 51 cm.

At the resection of the small intestine there were removed respectively 190 cm (No. 121), 122 cm (No. 105) and 134 cm (No. 118), measured immediately after the removal. At the autopsy there remained respectively 45, 82 and 80 cm of small intestine, measured from the duodenojejunal flexure to the site of the anastomosis. So the resection has involved respectively the distal *81, 60 and 63 % of the small intestine.*

The possibility cannot be excluded that the section of the small intestine remaining after the operation may have undergone a compensatory elongation. The proportion between the length of the resected gut before and after its removal has been about 200: 122. A side-to-side anastomosis was employed.

*Observation period:* 82 days (No. 121), 140 days (No. 105) and 146 days (No. 118).

*General experimental conditions:* Preoperative treatment for worms, diet, living conditions, technique of examination, etc. have been the same as previously.

## Clinical and Morphological Changes in the Animals.

*Experiment 1* (pup No. 121; observation period 82 days).

*Clinical changes:* Inhibition of growth, loss of appetite, emaciation and diarrhea, distinctly recognizable about 3 weeks after the operation. Then rapidly progressing aggravation of the general condition and extreme emaciation. From the 75th day the animal was flaccid and exhausted. About simultaneously with these clinical changes there developed a rather severe normochromic, ultimately hyperchromic, anemia with pronounced macrocytic tendency. *No* skin changes or clinical signs of an affection of the central nervous system. A gastric secretion was preserved. The animal died spontaneously.

**Table 1.**

*Dog. No. 121.*

| Date | Hb. % | Red blood cells in mill. | White blood cells | Color index | Volume % | Reticulocytes ‰ | Diameter of red blood cells | | | Size of animal | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Minimum μ | Maximum μ | Average μ | Length cm | Weight kg |
| 22/2 40 | 82 | 5.71 | 16,680 | 0.72 | 35 | | 6.0 | 8.0 | 6.81 | 53 | 5,700 |
| » | Operation | | | | | | | | | | |
| 28/3 40 | 82 | 5.39 | 56,480 | 0.76 | 40 | 3 | 5.0 | 8.0 | 6.56 | 55 | 5,150 |
| 30/4 » | 56 | 4.06 | 61,560 | 0.69 | 35 | 10 | 5.0 | 9.5 | 6.68 | | |
| 7/5 » | Bone-marrow puncture (femur) | | | | | | | | | | |
| » | 56 | | | 0.69 | | | 5.0 | 9.5 | 6,62 | | 4,200 |
| 9/5 » | 52 | 2.91 | 35,680 | 0.88 | 22 | 50 | 5.5 | 9.0 | 6.98 | | |
| 13/5 » | Died. | | | | | | | | | | |

As to the results of the blood examinations, functional stomach test, measure and weight, see Tables 1 and 4.

Intravital bone-marrow puncture (femur), on the 76th day: Moderately hyperemic and markedly oedematous, cellular marrow, containing rather many fat cells. After this, injection of liver extract, intramuscularly, for 4 days, 3 $cm^3$ of Hepsol daily, without any effect whatever.

*Morphological Changes. Macroscopic:* Peritoneum and site of anastomosis appear normal. Length of the small intestine from the duodenojejunal flexure to the site of anastomosis, 38 cm; herefrom to the ileocoecal valve, 7 cm. Mucous membrane of the digestive canal appearing normal. Other organs normal.

*Microscopic:* Bone marrow of vertebral bodies fairly rich in cells, moderately hyperemic and markedly oedematous; femoral marrow containing but scanty cells, moderately hyperemic, markedly oedematous, with remnants of fat cells; tibial marrow free from cells, otherwise appearing like the femoral marrow.

*Central nervous system*[1]*:* Sections from the spinal cord (cervical and lumbar): Several anterior horn cells moderately swollen, with chromatolysis and, in a few cells, vacuoles; some of the cells were shrunken, in part typically sclerotic. Medulla oblongata, pons and corpora quadrigemina: Cellular changes increasing in extent, in particular, increased number of sclerotic cells; besides, in a few instances, cellular changes corresponding to »Nissl's schwere Zellkrankheit»; distinct microglia reaction. Pronounced oedema of the pons. Cerebellum: Changes in the nucleus dentatus similar to the above-mentioned in nature and degree. A considerable part of the Purkinje cells had undergone some changes; many were swollen, more or less indistinct; a smaller number were shrunken. Basal ganglia: The horn of Ammon showed swelling as well as sclerosis of the ganglion cells, also vacuolization. Here, however, the changes were less pronounced than in the two preceding sections of the brain. The other ganglion cell groups showed an unequal distribution of similar changes together with normal cells. Cortex cerebri: No definite abnormalities.

Some of the lymph glands: Moderate phagocytosis and scanty giant-cell formation in the sinuses, some plasma cells, moderate hemosiderosis. Other lymph glands appeared almost normal. Spleen and liver: Hemosiderosis, very marked in the spleen, moderate in the liver. Tongue: Slight subacute, inflammatory infiltration of the mucous membrane. Other organs: No changes.

*Experiment 2* (pup No. 105; observation period 140 days).

*Clinical changes:* Rather soon after the operation there were noticed an inhibition of growth, some emaciation, moderate loss

[1] Staining *methods: Hematoxylin-eosin*, v. Gieson, Einarson, Wolter-Kulschitzky.

**Table 2.**

*Dog No. 105.*

| Date | Hb % | Red blood cells in mill. | White blood cells | Color index | Volume % | Reticulocytes ‰ | Diameter of red blood cells | | | Size of animal | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Minimum μ | Maximum μ | Average μ | Length cm | Weight kg |
| 6/7 39 | 80 | 5.86 | 12,560 | 0.68 | 48 | 1 | 6.5 | 8.5 | 7.35 | 48 | 6.6 |
| 7/7 » | Operation | | | | | | | | | | |
| 17/8 » | 52 | 4.08 | 24,840 | 0.64 | 31 | 9 | 6.5 | 8.5 | 7.34 | 61 | 6.85 |
| 30/8 » | 73 | 5.38 | | 0.68 | | | 6.0 | 8.5 | 7.57 | | |
| 6/9 » | 76 | 5.13 | 14,880 | 0.74 | 35 | 4 | 6.0 | 8.5 | 7.30 | | 6.0 |
| 22/9 » | 78 | 4.88 | 12,680 | 0.78 | 38 | 4 | 6.5 | 8.5 | 7.17 | | |
| 6/10 » | 69 | 5.04 | 18,280 | 0.68 | 37 | < 1 | 5.5 | 8.0 | 7.01 | 63 | |
| 20/10 » | 82 | 5.14 | 10,680 | 0.80 | 38 | 3 | 5.5 | 8.0 | 6.96 | | |
| 6/11 » | Second Operation | | | | | | | | | | |
| 21/11 » | 69 | 4.22 | 36,240 | 0.82 | 36 | 2 | 6.0 | 8.5 | 7.16 | | 6.0 |
| 23/11 » | Died. | | | | | | | | | | |

of appetite and persistent diarrhea. Still the animal was lively and apparently feeling well. Signs of intense universal itching appeared on the 17th day. Beginning symmetrical loss of hair appeared at the root of the ear and on the extremities on the 23rd day. After the 32nd day there was a rather sudden aggravation of the condition of the animal, especially with noticeable emaciation, increasing symmetrical loss of hair on the trunk and, in particular, on the head, ears and extremities. Now the skin was also eczematous. Later the paws became oedematous, reddish. No pigmentation of the skin. Gait stiff and cautious. But the animal was still lively. On the 55th day a clinical subremission commenced, and it progressed rapidly in the following weeks. On the 119th day the animal was, on the whole, normal, although still presenting a slight leanness and defective hirsute of the ears, round the eyes and on the paws. The consistency of the feces varied between mushy and normal.

During the course of illness a slight degree of anemia was ascertained, varying a little, at first of normochromic type, later hyperchromic; slight macrocytic tendency before the appearance of the subremission. Achylia was present from the 36th to 119th day.

In view of previous experiences it was reasonable to assume that the fundus region of the stomach had taken an active part in the spontaneous subremission. So, in the hope of being able to reproduce

the pellagra, subtotal resection of the stomach was performed on the 123rd day after the operation ($^{6}/_{11}$—39), leaving a part of the pylorus together with the cardia; end-to-end anastomosis. After this operation the animal became debilitated rather rapidly, and died spontaneously 18 days later without having presented any particular clinical changes.

For the results of the blood examinations and functional stomach tests, measures and weights, see Tables 2 and 4.

*Morphological Changes. Macroscopic:* Some fibrillary peritoneal adhesions round the spleen. Intestinal anastomosis adequate. Gastric anastomosis a little narrow. Length of the small intestine from the duodenojejunal flexure to the site of the anastomosis, 75 cm; herefrom to the ileocoecal valve, 7 cm. A few enlarged abdominal lymph glands. Mucous membrane of the digestive canal normal. Other organs normal.

*Microscopic:* Bone marrow of vertebral bodies fairly rich in cells, markedly hyperemic and oedematous; femoral marrow containing but scanty cells, very hyperemic and markedly oedematous; tibial marrow free from cells, otherwise appearing like the femoral marrow.

*Central nervous system:* In the spinal cord the majority of the ganglion cells had undergone some changes. The largest cells were chiefly swollen, in variable degree, with occurrence of the most severe forms of degeneration; sclerosis more frequent in the smaller cells. Medulla oblongata, pons and corpora quadrigemina: Here, too, a majority of the cells had undergone some changes; besides, there were numerous instances of »Nissl's schwere Zellkrankheit»; also complete deterioration of several cells (»chadows»). Cerebellum: The nucleus dentatus showed almost exclusively swelling and effacement of the ganglion cells; nearly all the Purkinje cells had changed, being either swollen and effaced, or shrunken and dark-staining, with concentration of the nucleus; vacuolization seen in both forms of altered cells. Basal ganglia: A considerable part of the cells showed sclerosis or, especially, swelling. Cortex cerebri: Extensive cellular changes in all the layers, moderate swelling as well as shrinkage approaching sclerosis.

Lymph glands and spleen: Hemosiderosis, variable in the lymph glands, slight in the spleen; one lymph gland showed a couple of subchronic abscesses. Tongue: Moderate acute inflammation of

the mucous membrane. Testis: No spermatogenesis. Skin: Moderate hyperkeratosis and scattered, small, subacute abscesses. Other organs: No changes.

*Experiment 3* (pup No. 118; observation period 146 days).

*Clinical changes:* About 2 weeks after the operation, inhibition of growth was noticed. The feces were alternatingly mushy or thin; later, almost continuous brownish-grey diarrhea. Appetite and nutrition still good. Progressing universal skin changes (from the

Table 3.

*Dog No. 118.*

| Date | Hb % | Red blood cells in mill. | White blood cells | Color index | Volume % | Reticulocytes % | Diameter of red blood cells | | | Size of animal | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Minimum μ | Maximum μ | Average μ | Length cm | Weight kg |
| 30/1 40 | 84 | 5.09 | 16,080 | 0.82 | 33 | 12 | 6.0 | 8.0 | 6.99 | 51 | 7,800 |
| 1/2 » | Operation | | | | | | | | | | |
| 28/2 » | 75 | 5.46 | 18,040 | 0.68 | 35 | 11 | 6.0 | 8.0 | 7.27 | | |
| 28/3 » | 80 | 5.33 | 14,400 | 0.75 | 41 | 21 | 6.0 | 8.5 | 7.16 | 59 | 7,130 |
| 30/4 » | 58 | 4.41 | 19,160 | 0.66 | 32 | 6 | 6.5 | 9.5 | 7.78 | | |
| 7/5 » | Bone-marrow puncture (femur) | | | | | | | | | | |
| » | 69 | | | | | | 6.5 | 10.0 | 7.78 | | |
| 30/5 » | 56 | 3.11 | 13,120 | 0.90 | 26 | 9 | 7.0 | 9.5 | 7.90 | | |
| 3/6 » | 52 | 3.33 | 8,600 | 0.78 | 26 | 13 | 6.5 | 9.0 | 7.81 | | 6,400 |
| 10/6 » | 48 | 3.09 | 15,880 | 0.78 | 25 | 2 | 6.0 | 9.0 | 7.53 | | |
| 17/6 » | 48 | 2.76 | 23,680 | 0.87 | 25 | 28 | 7.0 | 9.5 | 7.92 | | |
| 25/6 » | Died. | | | | | | | | | | |

75th day) in the form of numerous asymmetrical denuded spots. At the same time the skin of these bare areas became thickened, folded, eczematous, fissured, and moist, but later mostly dry. Simultaneously with these changes the appetite was decreasing and the nutrition getting poor. 124 days after the operation the skin changes covered about one half of the body surface. Evidence of itching, further emaciation in spite of a fairly good appetite. Gait stiff and cautious. Vision impaired. Finally the dog was lying still and died spontaneously. After the 91st day there was a gradually progressing, finally rather severe anemia, which originally was hypochromic, later temporarily hyperchromic, with early appearing, persisting, rather marked macrocytosis. Gastric secretion normal, at times

increased, but achylia demonstrated shortly before death. No subremission was observed.

For results of the blood examination and functional stomach tests, weights and measures, see Tables 3 and 4.

Intravital bone-marrow puncture (femur) on 97th day: Cellular marrow, containing fat cells, alternating with fatty marrow poor in cells; moderate hyperemia and oedema; slight increase in amount of plasma cells.

**Table 4.**

*Test meals.*

| Dog No. 121 | | | | Dog No. 105 | | | | Dog No. 118 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Date | Amount cm³ | Congo | Phenolphthalein | Date | Amount | Congo | Phenolphthalein | Date | Amount | Congo | Phenolphthalein |
| 22/2 40 | 33 | 18 | 30 | 27/7 39 | 10 | 30 | 82 | 30/1 40 | 7 | 26 | 42 |
| 2/3 » | 17 | 50 | 72 | 11/8 » | 2 | 0 | | 12/2 » | 5 | 42 | 54 |
| 20/3 » | 10 | 52 | 67 | 22/8 » | 115 | (+) | 130 | 2/3 » | 14 | 34 | 41 |
| 9/4 » | 13 | 60 | 95 | 8/9 » | 30 | 0 | 185 | 20/3 » | 15 | 14 | 19 |
| 23/4 » | 34 | 11 | 46 | 10/10 » | 3 | 0 | 15 | 2/4 » | 4 | 50 | 58 |
| | | | | 2/11 » | 17 | 31 | 59 | 23/4 » | 14 | 90 | 109 |
| | | | | | | | | 7/5 » | 10 | 48 | 64 |
| | | | | | | | | 21/5 » | 20 | 46 | 57 |
| | | | | | | | | 20/6 » | 4 | 0 | 55 |

*Morphological Changes. Macroscopic:* Some fibrillary peritoneal adhesions. Site of anastomosis looking natural. Length of the small intestine from the duodenojejunal flexure to the site of the anastomosis, 75 cm; herefrom to the ileocoecal valve, 5 cm. At the coecum, a conglomerate of rather firm lymph glands, measuring 2.5 × 2 × 1 cm. Mucous membrane of the digestive canal normal. Other organs normal.

*Microscopic.* Bone marrow of vertebral bodies containing only a moderate amount of cells in general, but relatively many plasma cells; moderate hyperemia and oedema. Femoral marrow very markedly hyperemic and oedematous, containing a moderate amount of cells with relatively many plasma cells; tibial marrow like the femoral.

*Central nervous system:* In the spinal cord nearly all the ganglion cells had undergone degeneration, some of them being from moder-

ately to greatly swollen, often vacuolized, with marked nuclear changes, and a few cells being shrunken or quite sclerotic; but most of the cells were changed as in »Nissl's schwere Zellkrankheit». Numerous »cellular shadows». Strong microglia reaction throughout. Probably extensive medullary sheath degeneration. Medulla oblongata, pons, corpora quadrigemina: Similar changes as in the spinal cord. Marked oedema of the pons. Glia reaction strongest in the corpora quadrigemina. Cerebellum and nucleus dentatus: Similar changes as mentioned above. Nearly all the Purkinje cells had undergone some changes, some being more or less swollen or entirely undefinable, others being shrunken, deeply staining even far out in the dendrites; here the nuclei were also deeply staining. Basal ganglia: Extensive swelling of the cells in the horn of Ammon; in the other basal ganglia most of the cells came near the picture of »Nissl's schwere Zellkrankheit». Cortex cerebri: Extensive degeneration of cells in all the layers, mostly swelling and »Nissl's schwere Zellkrankeit», seldom sclerosis.

Spleen and lymph glands: Slight hemosiderosis, marked diffuse, mostly extrafollicular, plasma cell infiltration; also moderate acute and chronic inflammatory infiltration in and around the conglomerate of lymph glands at the ileocoecal valve. Liver: No hemosiderosis, slight periportal plasma cell infiltration. Kidney: Slight diffuse parenchymatous degeneration (?). Small intestine: Slight diffuse infiltration of the mucosa with lymphocytes and especially plasma cells; no acute inflammation or ulceration. Skin: Moderate — severe hyperkeratosis and several small, partly confluent, abscesses [with remnants of parasites (?)]. Other organs apparently normal.

*Recapitulation.*

In 3 pups the resection of the distal 60—81 % of the small intestine has brought about a severe, subacute or chronic, fatal *symptom complex*, which *clinically* was characterized by: inhibition of growth, emaciation, skin and hair changes, anemia, and diarrhea. This affection was accompanied by morphological changes, especially in the central nervous system. The *anemia* was moderate or fairly severe, of normochromic or hypochromic type, later temporarily or more persistently of hyperchromic type, with more or less pronounced macrocytic tendency (Nos. 121 and 105,

respectively), or of distinctly macrocytic type (Nos. 118). After a latent period of a couple of weeks, a chronic *diarrhea* developed in all 3 cases; independent of this there was a transitory or terminal *achylia* (in the two chronic cases).

*Morphological findings:* From moderate to very severe *degenerative changes in the entire central nervous system*, most pronounced in the brain stem and medulla oblongata with acute (No. 121) or mostly chronic (Nos. 105 and 118) forms of ganglion cell degeneration; markedly hyperemic, oedematous and *hypoplastic bone marrow* (particularly in Nos. 121 and 105); slight or severe *hemosiderosis* of lymph glands, spleen and, in part, the liver too; moderate acute — subacute *glossitis* (Nos. 121 and 105); *hyperkeratosis and confluent small abscesses of the skin* (Nos. 105 and 118); no spermatogenesis. A striking feature was the appearance of moderate or severe *plasma cell infiltration* of the liver, intestinal mucosa, bone marrow and especially lymph glands and spleen (No. 118).

Apart from the anemia and diarrhea, then, this symptom complex shows considerable resemblance to the pellagrous picture observed constantly in our previous resection experiments. A subacute, progressive, somewhat atypical form of pellagra developed in 82 days in that animal on whom the resection of small intestine had been most extensive. A chronic, more typical, form of pellagra developed in the 2 other animals, with an observation period of 140—146 days; in one of these dogs there was a clinical subremission of the pellagrous condition.

It is to be pointed out that in no case did the resection of this large distal section of the small intestine bring about any clinical or morphological changes that might be attributed, for instance, to avitaminosis A, C or D.

## Forms of Experimental Endogenous Pellagra.

With the experiences gained from the simple and combined resections of stomach and intestines we have carried out for some years, it is practicable now to set up *three forms of endogenous pellagra:* gastroprival, pyloro (duodeno) prival and »enterogenous».[1]

[1] In order to settle whether this form of pellagra is specifically ileoprival, experimental studies are now being carried out with resections of the jejunum.

Clinically there is a fundamental similarity between these three forms, but each of them has its own well-characterized features from qualitative, quantitative and processive differences.

1. The *gastroprival type* represents the most severe form of the disease. It is either subacute or chronic (yet qualitatively uniform) progressive, constantly fatal and characterized by: *arrest* of growth, severe emaciation, eczematous skin, symmetrical loss of hair, degenerative changes in the central nervous system, and changes in the blood in the form of simple anemia, »isolated hypochromia» or polycytemia, besides hypoplasia of the bone marrow.

2. The *pyloro-duodeno-prival type* appears in two different forms.

*a*. The more frequent form, chronic, usually milder and more protracted, not always fatal. This form presents some of the symptoms of gastroprival pellagra and some special symptoms. The features of this disease are: *inhibition* of growth, emaciation, eczematous skin, symmetrical loss of hair, degenerative changes in the central nervous system, and changes in the blood in the form of hypochromic anemia or »isolated hypochromia» (in 2 out of 7 cases with macrocytic characteristics). In addition, there are the following changes which are specific as to the localization: achylia, tendency to subremission, alopecia areata-like loss of hair, pigmentation of the skin and hyperplasia of the bone marrow.

*b*. A less frequent, acute or subacute fatal form which is atypical as it is stamped almost exclusively by severe anemia and severe *morphological* changes in the central nervous system.

3. The *»enterogenous type»* which may be characterized as a combination of the pyloroprival form (although without the specific form of loss of hair and pigmentation of the skin, and with hypoplasia of the bone marrow instead of hyperplasia) and certain specific changes depending on the localization: anemia of macrocytic hyperchromic character and chronic diarrhea (together with glossitis, hemosiderosis, etc.).

The condition resulting from combined resection of the pylorus + the Brunner gland section + the distal two-thirds of the small intestine falls under the »enterogenous» type.

## On the Causal Aspects of the »Enterogenous» Symptoms.

In comparison with our previous resection experiments, in spite of the difference of the mucous membranes removed, isolated resection of the small intestine is thus found to have produced fundamentally the *same endogenous pellagra* as did resection of the pylorus + the Brunner gland section of the duodenum + the distal two-thirds of the small intestine (Petri, Jensenius & Thyssen, 1941) and as resection of the pylorus + the Brunner gland section alone (cf. the review of our previous experiments and new ones by Petri, Nørgaard & Jensenius, 1941).

The *special changes* — hyperchromic, macrocytic anemia, hypoplasia of the bone marrow and diarrhea — which the combined resection of the pylorus, duodenum and small intestine has shown a tendency to produce, have appeared to be of the same nature and even accentuated in degree after isolated resection of the small intestine. On the other hand, this form of the lesion is never seen after resection of the pylorus + the Brunner gland section alone. *So these special changes constitute a specific »enterogenous» phenomenon.*

According to the prevailing view as to the cause of pellagra, it is to be expected that the experimental »enterogenous» pellagra will be ascribed to elimination of a section of the small intestine important to the absorption or metabolism of vitamin B (»pellagra from primary defective absorption»). Causally this form would thus be in contrast to the gastroprival (or pyloroprival) pellagra we have produced previously (»pellagra from secondary defective absorption»). The correction of such an assumption is contradicted directly, however, by the fact that gastroprival pellagra is a more severe (more typical, never subremittent) form of the illness than is the »enterogenous».

According to our not yet concluded, systematic studies of the causal aspects of experimental endogenous pellagra, a specific anti-pellagra factor appears to be associated with the function of the stomach (fundus?) (Petri and collaborators, 1938—40). On the background of this hypothesis there are theoretically two possible explanations of the etiology of the »enterogenous» pellagra: 1) the resection of the small intestine may have prevented the further

formation, or the absorption, of a specific endogenous antipellagrous product; 2) or the resection may have eliminated some quality of the small intestine that is of regulatory importance to the gastric secretion (and hence to the antipellagrous factor).

Until further experiments with resection and therapy have been carried out, we shall merely be able to theorize also concerning the cause of the special changes and their possible connection with the pellagra. In view of the experiences from the human pathology, the appearance of the special type of anemia will either be ascribable to lacking absorption or production of substances that ordinarily counteract macrocytosis and hyperchromia (antipernicious-anemic principle, vitamin B), or they may be attributable to a possibly toxic effect (on the liver or on the bone marrow) that is related to the chronic state of diarrhea.

It may seem obvious to attribute the *chronic diarrhea* to the great reduction in the lenght of the small intestine, but this is gainsaid by the appearance of the diarrhea after a latent period of a couple of weeks. Further, the condition of the site of the anastomosis and the appearance of the mucous membrane go against the possibility that the diarrhea might have been due to secondary changes in the remaining proximal part of the small intestine. Nor does it seem reasonable to look upon the achylia as any important factor in the production of this diarrhea. For the achylia was pronounced only in one case, and in previous experiments diarrhea was observed only as a terminal phenomenon after total gastrectomy (or resection of the pylorus + the Brunner gland area which was followed constantly by secondary achylia); besides, after resection of the small intestine alone, there has been no chronological consistency between the appearance of the achylia and that of the diarrhea. Moreover, our previous resection experiments go against the possibility that the diarrhea might be a symptom of pellagra. On the other hand, the tendency of the diarrhea to improve at the time of the clinical subremission of the »enterogenous» pellagrous condition is suggestive of an etiological relation. Finally, there is the theoretical possibility — which the experiments now going on, with resection of proximal sections of the small intestine, appear to substantiate — that the distal part of the small intestine normally is associated with some physiological function, preventive of diarrhea.

## To What Lesions in the Human Pathology is the »Enterogenous» Symptom Complex Comparable?

Operatively this condition has to be classified with certain previously reported cases of *intestinal resection in man.* Thus, Ryti (1927), Glatzel (1929), and Sturgis & Goldhamer (1939) have each reported one case in which the small intestine was resected [222 cm (Ryti), about 120 cm (Sturgis & Goldhamer)] on account of post-operative ileus or adhesions. After respectively 4, 5 and 5 years, hyperchromic or macrocytic anemia and hypochylia or achylia developed. Clinical neurocutaneous changes are not mentioned by these authors, perhaps they were overlooked, or they may not have developed to any noticeable degree as these patients were adult at the time of the operation. Genetically it is worth noticing that there is a parallellism between these operations and our resections of the small intestine with regard to the type of anemia and also to the tendency to hypofunction of the stomach.

In view of the chronological appearance and degrees of the symptoms, the experimental »enterogenous» symptoms may be said clinically + morphologically to correspond mostly to sprue or to *pernicious-like cases of endogenous pellagra.* In several respects, moreover, the symptom complex shows some resemblance to pernicious anemia, but hyperplasia of the bone marrow is absent, and further, we do not yet know how such animals will react to a systematic specific antipernicious-anemic therapy.

Localizationally + clinically there is a particularly conspicuous resemblance to the special features of *terminal ileitis* as described by Plum & Warburg (1939). Chronic inflammation of the ileum in man thus appears to be able to cause the same clinical picture as experimental resection of this gut in pups, indicating that a special function of the small intestine has been eliminated in both cases. Accordingly, it is hardly to be expected that an extensive resection of the ileum for terminal ileitis may result in the intended improvement of these particular symptoms.

## Summary.

A report is given on the results of isolated resection of 60—81 % of the distal part of the small intestine on 3 pups, with an observation period of 82, 140 and 146 days respectively.

There constantly developed a pellagrous, fatal symptom complex characterized by: inhibition of growth, emaciation, anemia of macrocytic and hyperchromic character, skin and hair changes, tendency to achylia, degenerative changes in the central nervous system, hypoplasia of the bone marrow, and chronic diarrhea. In one case there was a clinical subremission; in another case, a plasmacellular infiltration of various organs.

In type this »enterogenous» pellagra corresponds to our previous observations after resection of the pylorus + the Brunner gland area (with or without resection of the distal part of the small intestine). On the other hand, the type of anemia and the chronic diarrhea have to be characterized as specific of the resection of the small intestine.

A survey is given of the different forms of endogenous pellagra hitherto produced experimentally by the writers.

The causal aspects of the »enterogenous» symptom complex are discussed, and comparison is made between this lesion and certain conditions in the human pathology.

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# Anémie à type pernicieux chez un enfant de 9 mois.

Par

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(Ce travail est parvenu à la rédaction le 14 Août 1941).

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La plupart des anémies qui se rencontrent chez les jeunes enfants sont des chloro-anémies ou oligosidérémies: anémies microcytaires hypochromes, qui réagissent favorablement à un traitement martial. Ces anémies peuvent atteindre les degrés les plus aigus, et dans les cas où elles apparaissent conjointement avec une infection chronique — elles sont souvent combinées avec rachitisme — le tableau clinique de la maladie peut se développer dans le sens d'une anémie pseudo-leucémique (Jaksch-Hayem). Ce syndrome est généralement attribué à la réaction spécifique qui caractérise le système hématopoiétique des petits enfants.

D'autres formes d'anémies dans la première enfance sont rares; mais on peut de temps à autre trouver des anémies à type hyperchrome, le plus souvent sous forme d'une anémie hémolytique, qui généralement est familiale, mais qui peut aussi être acquise. Des cas certains d'anémie pernicieuse dans le premier âge n'a pas été décrits, les enfants les plus jeunes ayant eu entre 9 et 11 années. Récemment il aurait été relevé un cas (douteux — sans achylie) chez un enfant de 6 ans (Debré et collaborateurs).

Dans la littérature se trouve indiqué qu'on a souvent avantage à recourir à un traitement martial et hépatique combiné à l'occasion de certaines anémies septiques de la première enfance, où le traitement martial seul est inefficace. Cooley souligne spéciale

ment ce fait. Toutefois je n'ai réussi à trouver aucune description hématologique précise de semblables cas.

Au cours de ces deux dernières années, j'ai eu l'occasion d'observer un enfant qui, à plusieurs reprises, a subi une grave anémie en rapport avec de banales infections. L'anémie s'est montrée réfractaire au traitement martial, tout en réagissant promptement chaque fois à l'extrait de foie[1]. Le tableau hématologique montrait des mégaloblastes typiques et la moelle osseuse s'est avérée être — lors d'examens répétés — une moelle mégaloblaste caractérisée qui, après un traitement à extrait hépatique, s'est changée en moelle normoblaste. Voici l'histoire clinique, de l'enfant en question:

Roy, H. né le 1. 2. 38, hospitalisé à Ullevaal, VIII, le 9 novembre 38, (à l'âge de 9 mois).

La naissance avait eu lieu au terme normal et s'était passée normalement ainsi que les couches. La mère rapporta avoir été anémique pendant la grossesse, mais sur une enquête à la clinique gynécologique (Kvinneklinikken) où l'enfant fut mis au monde, on apprit qu'aucune remarque n'avait été faite quant à une pâleur extraordinaire chez la parturiante, et aucun examen de son sang n'avait été fait.

L'enfant fut uniquement nourri au sein jusqu'à l'âge de 7 mois. Par la suite il eut un supplément de biscuits trempés et de légumes en purée.

Le dernier mois avant l'hospitalisation son appétit était devenu moins bon, il avait commencé à rendre ses repas, était maussade et agité; les selles étaient laborieuses.

*Etat présent, le 9. 11. 38:* L'enfant est extrêmement pâle et un peu bouffi. Agité et criailleur. Développement normal pour son âge. Aucun signe de rachitisme (par radioscopie non plus). Poids 8,500 gr. Gorge injectée. Légère dilatation de la rate. Par ailleurs aucune altération pathologique n'a pu être constatée à un examen somatique ordinaire, à part une température de 38.2. On remarqua notamment qu'il n'y avait aucune altération de la langue.

*Examens de laboratoire:* L'urine contient constamment de l'albumine, avec quelques cylindres hyalines. Aucune augmentation de l'urée (Ur+ 20 mg%). Couleur du sérum: 2 (Meulengracht) WaR. +. *Examen du sang:* Hb 41 %. Globules rouges 2.12 mill., blancs 10,000. Un frottis montra des mégaloblastes typiques (v. fig. 1—2). Le calcul différentiel des globules blancs révéla une lymphocytose, ainsi que quelques rares myélocytes (½ %) — aucune déviation à gauche. Les globules rouges étaient bien saturés, généralement *grands*, aniso-poikilocytose considérable, avec quelques petits érotrocytes *en partie piriformes*, en partie sous forme de croissants, ou d'ellipses. Le repas d'epreuve d'Ewald révéla de l'achylie. Les parents et une soeur du malade également examinés avaient un état hématologique normale.

[1] NB sans fer.

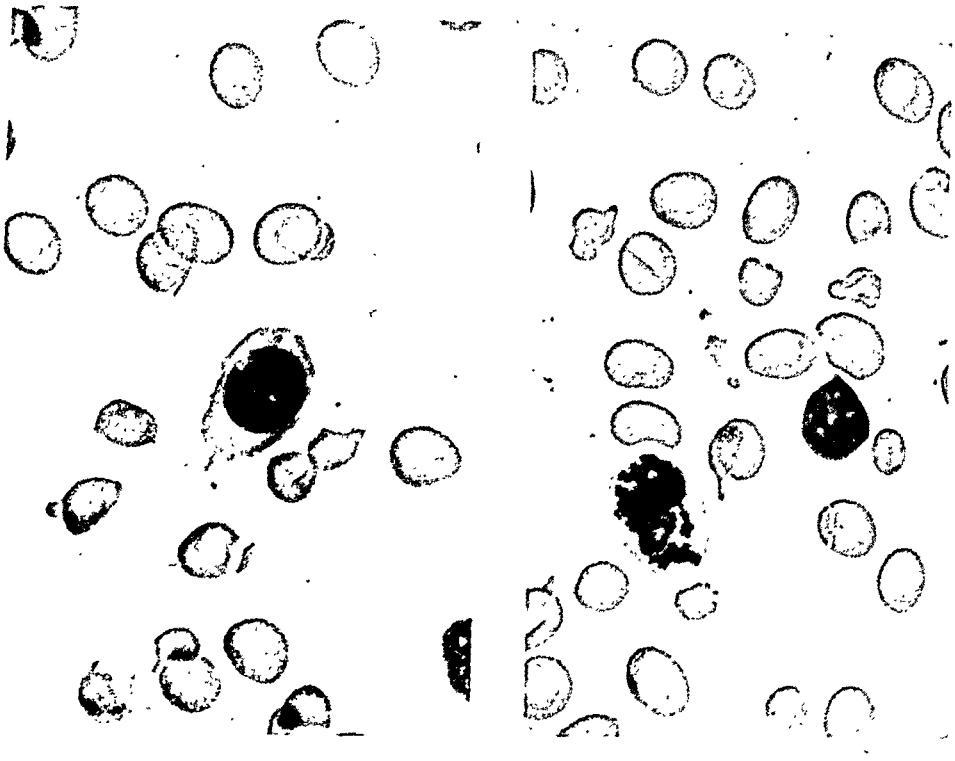


Fig. 1 a. Fig. 1 b.

Mégaloblastes dans le sang (11.11.38) (×1,000).

*Marche de la maladie:* Au cours de la première semaine du séjour à l'hôpital l'enfant était fébrile et assez éprouvé, avec des vomissements et peu d'appétit; peu à peu la température est revenu à la normale, mais l'enfant manquait toujours d'appétit, était faible et apathique. Il fut institué un traitement martial (Fe reduct. 0.25×2) et une légère augmentation de la valeur globulaire s'en suivit la première semaine, mais ensuite il y eut une constante diminution (voir tracé) et l'état général restait mauvais.

Le 22 décembre une ponction de la moelle osseuse fut entreprise (ds. le tibia) et l'hémomyélogramme montra une moelle mégaloblaste caractérisée (Fig. 3). L'enfant reçut alors pendant deux jours consécutifs 5 cm³. pernami (Nyco), administrés intra-musculairement, et ceci entraîna un changement complet dans l'état du petit malade. Il se mit à manger, fut vif et gai. Les valeurs globulaires augmentaient régulièrement pendant environ un mois et l'enfant put être renvoyé de l'hôpital dans un état de bien-être, le 3 février 1939.

*2:e séjour à l'hôpital.* — L'enfant resta bien portant les premiers 8 jours après son exéat. Le 15 février il fut enrhumé, rhume du cerveau et toux. Le 28. 2. il alla plus mal, devint échauffé et eut la respiration précipitée. Temp. 39.2. Exsudation des deux oreilles. Rentré à l'hôpital, service VIII, le 3. 3. 39.

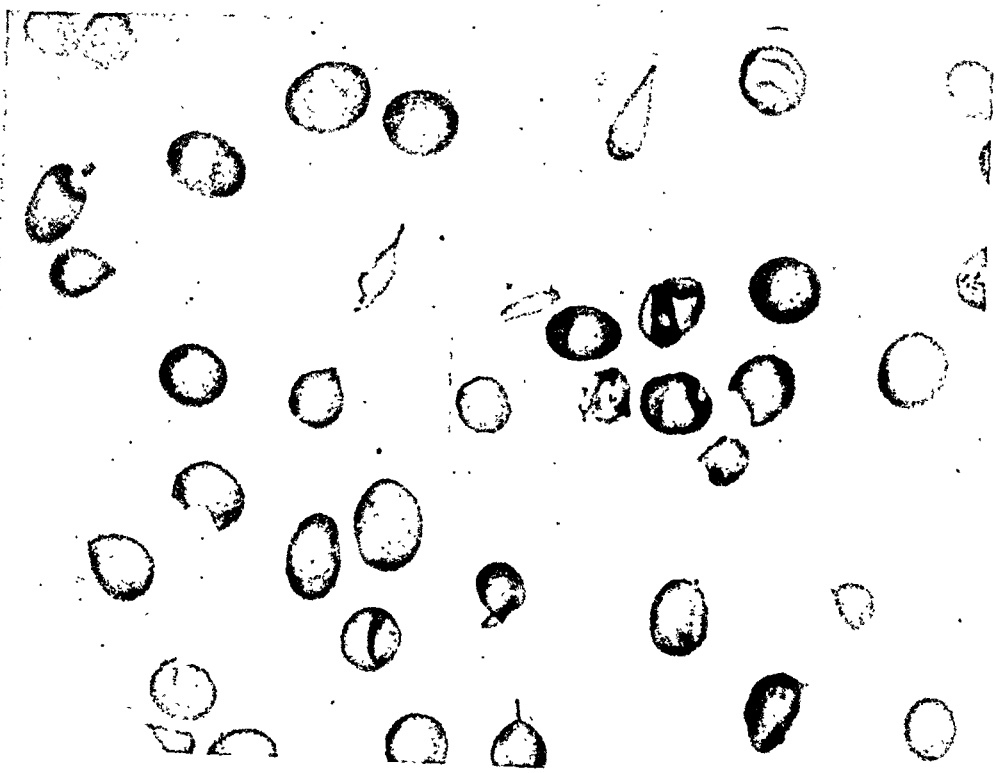


Fig. 2: Erythrocytes piriformes, en formes de croissants ou d'ellipses.

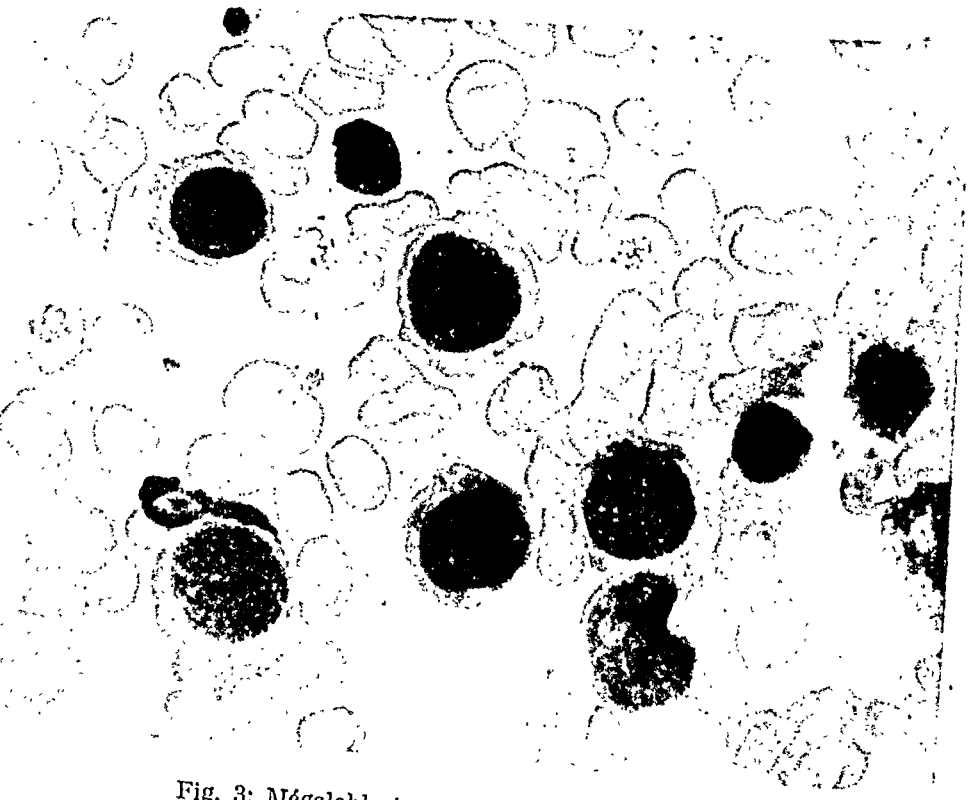


Fig. 3: Mégaloblastes dans la moelle osseuse.

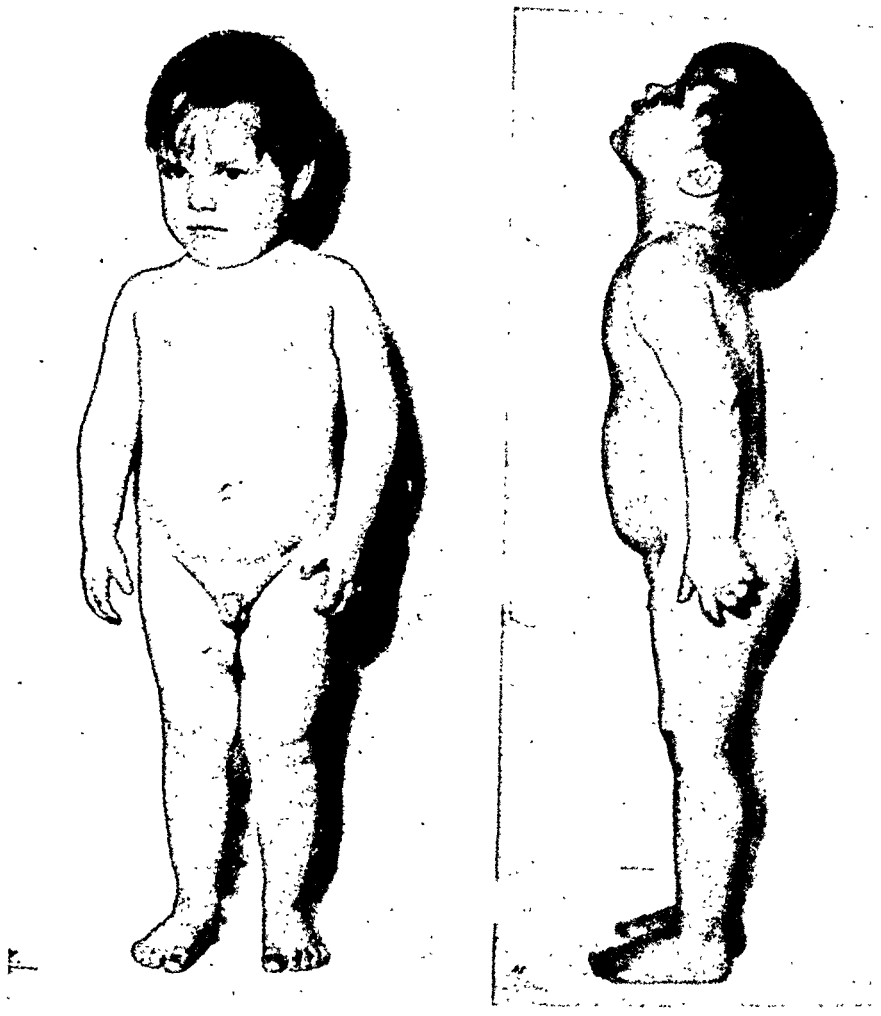


Fig. 4: Roy H. à trois ans.

*Etat présent* le 3. 3. 39: L'enfant est fort éprouvé. Temp. 39.5, respectivement 40; pouls 114,

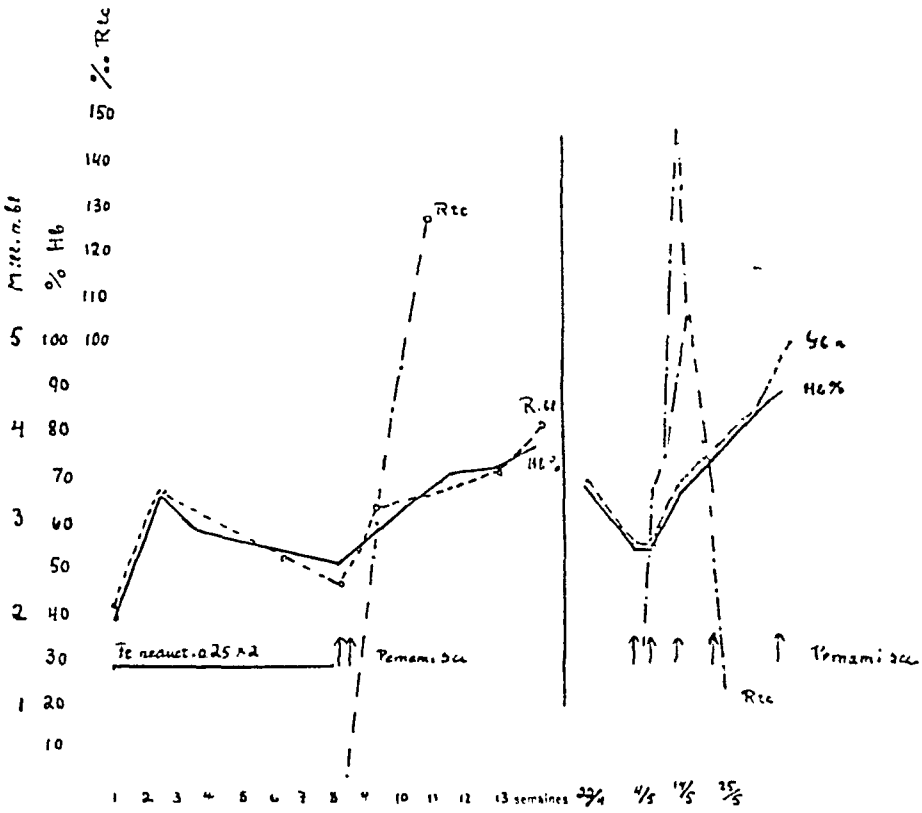
Exsudation purulente des deux oreilles. Sur le poumon s'entendent des râles sibilants (sibili) et de nombreuses petites bulles. Faible dilatation de la rate. Urine alb.+. Examen hématologique: Hb 76 %, Gl. r. 4.3 mill. bl. 7.200. Un frottis montra le même tableau qu'au moment de la première hospitalisation: aniso-poikilocytose notable avec de grands gobules rouges bien saturés; les globules blancs révélèrent une déviation à gauche avec granulation toxique.

*Marche de la maladie:* L'enfant fut traité au moyen de sulfapyridine, 0.5 g journellement pendant 3 jours (3 fois 24 h.). Il en résulta une baisse de la température, mais le 11. 3. celle-ci augmenta de nouveau, et l'enfant resta quelques jours avec une température intermittente, entre 39.6

et 36. Il fut de nouveau soumis à un traitement de sulfapyridine, 0.5 g p. d. pendant une semaine, et fut par la suite afébrile (v. tracé).

Comme lors de son premier séjour, l'enfant fut d'abord soumis à un traitement martial: Fe reduct. 0.25×2. Les valeurs hématologiques diminuaient cependant, et l'état général restait mauvais, l'appétit lamentable.

Une ponction de la moelle osseuse montra, comme la dernière fois, une moelle mégaloblaste caractérisée. Un traitement à extrait hépatique fut de nouveau institué, et il s'en suivit une augmentation des réticulo-




cytes jusqu'à 14.6 %, cependant que l'hémomyélogramme se changea de mégaloblastose en macronormoblastose (v. courbe).

Fèces étaient pendant les deux séjours normales et la courbe glycémique avait une allure normale.

L'enfant sortit de l'hôpital en mai 1939, et resta en bonne santé pendant un an. Un contrôle ultérieur des valeurs hématologiques montra celles-ci légèrement réduites: Hb 80 %, gl.r. 3.72 mill. (taux gl. 1.08) le 6. 5. 40. L'enfant eut de la marmite et en prit journellement ½ cuiller à café×3. Le 11. 6. 40 il tomba malade des varicelles et les valeurs hématologiques baissaient régulièrement au cours d'un mois de 74 %, 3.58 mill., à 47 %, 2.24 mill. L'état général était maintenant mauvais, l'appétit nul. 10 cm³ de pernami amenèrent immédiatement une

Tableau.

| Date | Hb % | Gl.R. | Gl.Bl. | P. N. | Myeloc. | Segm. | | Lymf. | Mon. | Indiff. |
|---|---|---|---|---|---|---|---|---|---|---|
| 11.11.38 | 41 | 2.12 | 10,000 | | ½ | 2.5 | 17.5 | 72.5 | 2.5 | 3.5 |
| 22.11.38 | 67 | 3.86 | 8,000 | | | | | | | |
| 30.11.38 | 60 | | | | | | | | | |
| 24.12.38 | 52 | 2.78 | | 1 | | | | | | |
| 7. 1.39 | 65 | | | 1 | | | | | | |
| 13. 1.39 | 72 | 3.96 | 16,400 | | | | | | | |
| 24. 1.39 | 73 | | | | | | | | | |
| 3. 2.39 | 77 | 4.23 | 14,200 | | | | | | | |
| 7. 3.39 | 76 | 4.3 | 5,400 | | ½ | 11.5 | 10.2 | 73.2 | 3.2 | 3 |
| 7. 4.39 | 69 | 4.18 | 12,600 | | ½ | 6.5 | 22.6 | 61. | 8. | 1.5 |
| 22. 4.39 | 69 | 3.55 | | | | | | | | |
| 2. 5.39 | 56 | 2.83 | | 1 | | | | | | |
| 7. 5.39 | 56 | 2.83 | | 1 | | | | | | |
| 13. 5.39 | 67 | 3.37 | | 1 | | | | | | |
| 22. 5.39 | 74 | | | 1 | | | | | | |
| 25. 5.39 | 80 | | | | | | | | | |
| 30. 5.39 | 85 | | | | | | | | | |
| 2. 6.39 | 89 | | | 1 | | | | | | |
| 13. 6.39 | 89 | | | | | | | | | |
| 11. 7.39 | 90 | 5.03 | 8,200 | | ½ | | 6 | 87 | 2 | 4.5 |
| 6. 5.40 | 80 | 3.72 | 23,400 | | | | | | | |
| 11. 6.40 | 74 | 3.58 | 8,900 | | | | | | | |
| 25. 6.40 | 66 | 3.18 | | | | | | | | |
| 10. 7.40 | 47 | 2.24 | 6,700 | 2 | | | | | | |
| 19. 7.40 | 69 | 3.57 | | | | | | | | |
| 23. 7.40 | 90 | 4.87 | | | | | | | | |
| 9.12.40 | 37 | 1.68 | 7,300 | 2 | | | | | | |
| 16.12.40 | 56 | 3.05 | 7,400 | | | | | | | |
| 14. 1.41 | 90 | 4.14 | 5,600 | | | | | | | |

Reticulocytes:

| | |
|---|---|
| 26.12.39 | 0.8 |
| 30.12.39 | 6.4 |
| 10. 1.40 | 12.8 |
| 4. 5.40 | 3.4 |
| 7. 5.40 | 6.9 |
| 10. 5.40 | 7.6 |
| 13. 5.40 | 14.6 |
| 16. 5.40 | 10.4 |
| 22. 5.40 | 6.8 |
| 25. 5.40 | 2.5 |

1 indique 5 cm³ d'extrait de foie (Pernami Nyco).

Les taux d'hemoglobine indiqués antérieurement à la date du 11.7.39 montrent des valeurs trop basses, l'appareil n'ayant pas été ajusté. Les valeurs indiquées depuis cette date sont evaluées d'après le standard de Haldane.

révolution dans le tableau pathologique, l'enfant prit de l'appétit et se remit. De l'hépaforte fut administré, une cuiller à pot tous les jours, et les valeurs hématologiques étaient 2 mois plus tard de 90 % IIb, 4.87 mill. de gl.r. Trois mois après une nouvelle rechute survint par suite d'un rhume avec épistaxis, et le 19. 12. les valeurs hématologiques étaient les suivantes: Hb. 37 %, gl. r. 1.68 mill. (taux gl. 1. 12). L'extrait de foie avait encore cette fois le même excellent effet.

*Epicrise.* Un garçon a été sous observation depuis l'âge de 9 mois jusqu'à ce jour, où il a 3 ans. Au cours de ce temps il a souffert, en tout 4 fois, d'une anémie considérable à type légèrement hyperchrome, qui a réagi à l'administration d'extrait de foie, mais non pas au traitement martial. Une ponction de la moelle osseuse montra, à deux reprises, une moelle mégaloblaste typique qui, après un traitement hépatique, se changea en moelle normoblaste. Après injection d'extrait de foie, une crise réticulocytaire caractérisée est survenue. L'enfant souffre d'achylie. Il n'a eu aucune stéatorrhée, la courbe de la résistance glycémique est normale, la croissance entièrement normale. Pendant tout ce temps une légère albuminurie a persisté sans azotémie. Actuellement, le 3. mars 1941, l'urine est normale. Un nouveau repas Ewald montre toujours de l'achylie. (Günsburg ÷).

## Discussion.

L'anémie est une affection extrêmement commune à l'âge puéril. La classification des anémies infantiles offre cependant certaines difficultés, à cause de la façon spéciale dont réagit l'enfant et notamment le nourrisson.

Comme on le sait, l'érythropoièse se fait, au cours de la dernière phase de la vie foetale, essentiellement des centres hématopoiétiques dans la rate et dans le foie. Lors de la naissance ces centres révoluent et leur activité est entièrement assumée par la moelle épinière. Si celle-ci est exposée à une surcharge, par ex. lors d'une anémie provoquée par une hémorragie, une infection, ou autre chose de semblable, les centres foetaux peuvent facilement être induits à reprendre leur fonction antérieure et commencer à produire des globules rouges et blancs qui sont versés dans le sang. Ce »type embryonal» de globules rouges est, suivant Naegeli, de l'ordre des mégalocytes. On risque ainsi un versement de jeunes cellules dans le sang, des cellules qui ressemblent absolu-

ment aux globules qu'on trouve chez les adultes quand on constate chez eux une anémie pernicieuse.

En ce qui concerne les globules blancs, on trouve d'une façon analogue des éléments cellulaires souches tels que des myélocytes, en partie aussi des promyélocytes. Rohr fait remarquer que ces centres extra-médullaires, et notamment le foie et la rate, sont en contact direct avec la circulation — ils se déversent directement dans les veines du sinus splénique et dans celles du foie. Il n'y a donc rien qui empêche que des cellules jeunes et peu développées soient ainsi versées dans le sang. Dans la moelle osseuse au contraire ces cellules sont retenues, parce qu'il leur manque la faculté de se mouvoir et que le sinus de la moelle osseuse est sans rapport avec la circulation du sang.

Selon Rohr ce serait donc de la rate et du foie que proviendraient les jeunes cellules mal mûrées qu'on trouve dans le sang lors d'une leucémie myélogène, et il est naturel de supposer qu'il en soit de même pour les genres de jeunes cellules qu'on découvre dans le sang du nourrisson dans des cas pathologiques.

Il est nécessaire de souligner ces faits, connus de tous ceux qui s'occupent beaucoup d'»hématologie infantile», mais dont on ne tient pas toujours suffisamment compte.

Une dilatation de la rate est fréquente dans la première enfance, surtout à l'occasion d'infections, et ce phénomène, constaté concurremment avec les changements dans le sang que nous venons d'indiquer, peut souvent induire le médecin en la tentation d'établir la diagnose de leucémie ou de pseudo-leucémie. Ainsi l'anémie décrite par von Jaksch sous la dénomination de »anemia pseudoleukemia infantum» comporte un ensemble des symptômes suivants: dilatation prononcée de la rate, dilatation du foie, anémie modérée à type normo- ou hypochrome, leucocytose grave avec apparition dans le sang périphérique de leucocytes peu mûres: myélocytes et promyélocytes, ainsi que de globules rouges nucléés. Ce genre d'anémie qui se rencontre chez des enfants rachitiques concurramment avec une maladie infectieuse chronique, est interprêté comme une anémie secondaire, infrachronique, souvent à type hémolytique (Cooley).

La forme la plus commune d'anémie infantile est l'anémie hypochrome qui est une chloro-anémie caractérisée (ou une oligosidérémie) qu'on trouve surtout chez des enfants nés avec un

dépôt insuffisant de chlore (jumeaux, enfants nés avant terme et enfants dont la mère a été anémique pendant la grossesse).

Si ces enfants anémiques attrapent une maladie infectieuse, celle-ci provoquera une décomposition accélérée du sang et l'anémie sera ainsi exacerbée avec quelquefois une réduction considérable des globules rouges. Ce fait est généralement attribué à une influence de la moelle osseuse, où l'on peut constater des modifications tantôt de nature hypoplastique — et alors le résultat sera une anémie hypoplastique ou aplastique telle qu'on le voit dans des cas de sepsis —, ou bien — et c'est peut-être le cas le plus fréquent — il se déclare une inhibition du processus ou de l'écoulement (Rohr) avec une moelle riche en cellules qui forme un contraste frappant avec l'anémie par ailleurs prononcée.

La chloro-anémie réagit habituellement d'une manière prompte à un traitement martial et à une nourriture appropriée. Il reste encore à savoir si l'apport de vitamines joue un rôle dans ce cas. Les vitamines C ne jouent guère un tel rôle dans les chloro-anémies qu'on avait d'abord cru et, en ce qui concerne celles du groupe B, il n'existe pas non plus des observations exactes qui puissent prouver qu'elles soient d'une importance considérable. Cooley souligne que le résultat de la thérapie par vitamines ne répond pas aux attentes, et qu'elle ne répond pas du tout aux résultats qu'on a pu obtenir lors d'expériences sur des animaux.

La plupart des pédiatres ont cependant pu faire cette expérience que certaines anémies ne réagissent point au traitement martial, ni à une diète appropriée. Cooley rapporte quelques exemples d'anémies infectieuses secondaires qui ont été réfractaires au fer, mais où une seule transfusion de sang ou l'administration d'extrait de foie ont suffi à ramener l'hématopoièse à une activité normale. Il estime que ce fait peut être attribué à un »lack of some building substance, which the baby normaly stores, and which is readily replaced by transfused blood». Il note que son traitement habituel des »anémies infectieuses» est maintenant un traitement martial et hépatique combiné.

A part ces anémies secondaires et hypochromes, nous devons compter avec un certain nombres d'autres formes d'anémies propres à l'âge puéril. Deux de celles-ci se présentent comme des affections congénitales: l'*érythroblastose* congénitale et l'anémie »primaire» congénitale. Ces deux formes sont extrêmement rares.

Parmi les anémies hyperchromes nous pouvons, d'après Fanconi, rencontrer les types suivants:

1. L'ictère hémolytique (Kugelzellenanemi, Minkowski — Chauffard).
2. L'érythroblastose (Cooley).
3. L'anémie à cellules sous forme de croissants (Sichelzellenanemie).
4. L'anémie hyperchrome du lait de chèvre.
5. L'anémie hyperchrome de la maladie coeliaque.
6. L'anémie elliptozytique hémolytique primaire (Fanconi).

Toutes ces anémies ont en commun l'hémolyse qui se manifeste par une accentuation de la couleur du sérum et par une élimination accrue d'urobiline dans l'urine et dans les féces. (Ces phénomènes peuvent cependant manquer, p. ex. dans la maladie coeliaque lors d'une suppression de la fonction hépatique (Rohr)).

Les trois genres d'anémies premièrement indiqués sont des affections nettement familiales, en partie aussi raciales (Sichelanemie, érythroblastose).

L'anémie décrite par Cooley ne se trouve pratiquement que chez des familles originaires des pays méditerranéens. Elle est très nettement caractérisée, et se manifeste par anémie, dilatation de la rate, ictère, apparence mongoloïde et difformation typique des os. Dans le tableau hématologique on trouve de nombreux globules rouges nucléés.

L'anémie à cellules de croissants ne se voit guère que chez les nègres.

Dans les cas d'anémie provoquée par une alimentation à lait de chèvre, on peut observer un tableau pathologique rappelant celui de l'anémie pernicieuse. La moelle osseuse peut dans ces cas prendre l'apparence caractéristique d'une moelle proérytro-mégaloblaste (Balde, Fanconi). L'anémie réagit très bien à l'administration d'extrait de foie, également de foie de chèvre, ce qui semble prouver qu'il ne s'agit pas d'une anémie de déficience (défaut d'un facteur in- ou extrinsèque au lait de chèvre), mais bien plutôt d'une influence toxique sur la moelle osseuse.

Conjointement avec la maladie de Gee-Herter, la maladie coeliaque, il peut se manifester, comme nous l'avons déjà indiqué, des anémies hyperchromes avec moelle mégaloblaste. Ces anémies réagissent favorablement à un traitement par extrait de foie.

Dans le cas d'anémie elliptocytique décrit par Fanconi, il s'agit d'un garçon qu'il avait eu sous observation depuis la naissance jusqu'à ce que, lors de la description, le garçon avait 11 ans. La maladie se manifestait comme une anémie chronique prononcée. Des mégaloblastes furent constatées dans la moelle osseuse, et après un traitement hépatique il survint un renversement en moelle normoblaste. Les globules rouges étaient pathologiquement déformés avec une anisopoikilocytose prononcée et de nombreux globules rouges elliptiformes. Il y avait en outre des signes d'hémolyse accrue.

Comme je l'ai déjà remarqué, une anémie pernicieuse dans la première enfance n'a pas été décrite de façon convaincante, les cas les plus jeunes ayant été des enfants de 9 et de 11 ans. Le cas d'anémie pernicieuse récemment décrit par Debré et collaborateurs, chez un enfant de 6 ans, semble quelque peu incertain. (Pas d'achylie).

Après cette rapide récapitulation, nous allons discuter la diagnose dans le cas qui nous occupe.

La possibilité d'une ictère hémolytique peut être écartée. Le tableau hématologique ne montre pas la sphérocytose si caractéristique pour cette maladie. La couleur du sérum est normale. Contre cette possibilité s'inscrivent également l'anamnèse familiale négative et le bon effet du traitement hépatique. Ainsi que Varadi l'a fait remarquer, l'extrait de foie agit plutôt dans un sens contraire dans les cas d'ictère.

La diagnose d'érythroblastose et celle d'anémie à cellules de croissant peuvent également être éliminées.

La description des modifications hématologiques de l'anémie elliptocytique de Fanconi ne convient pas non plus à notre cas.

Il n'y a enfin nul point d'appui pour la diagnose de la maladie coeliaque. L'enfant s'est développé d'une façon absolument normale (voir photo) n'a jamais eu de stéathorrée et la courbe glycémique est normale.

L'enfant a d'abord été nourri par la mère, ensuite il a eu une nourriture mélangée, et du lait de vache. L'anémie provoquée par le lait de chèvre est ainsi exclue.

Peut-on dans ce cas-ci risquer la diagnose d'anémie pernicieuse? L'anémie pernicieuse peut être interprétée comme une maladie de déficience pouvant se déclarer par suite d'un manque

d'apport, de résorption ou d'exploitation du principe anti-pernicieux. Dans l'anémie pernicieuse idiopathique il se constate un manque du facteur dit »Castles intrinsic factor». Il existe quelquefois des formes symptomatiques d'anémie pernicieuse où le facteur dit »extrinsic factor» fait défaut (l'anémie macrocytère tropique décrite par Wills?) ou bien encore où la résorption en est réduite (maladie coeliaque).

Notre cas offre une série des signes cliniques qui caractérisent l'anémie pernicieuse: anémie hyperchrome réagissant à l'extrait de foie par une crise réticulocytaire caractérisée et une amélioration des valeurs hématologiques. Dans la moelle osseuse se manifeste simultanément un renversement de moelle mégaloblaste en moelle macro-normoblaste. Il y a de l'achylie. Contre la diagnose en question s'inscrivent tout d'abord l'âge de l'enfant et le fait qu'il n'y a eu aucun signe d'hémolyse accrue.

Il n'y a aucune raison de croire que cette anémie d'apparence pernicieuse soit due à un défaut de résorption. L'enfant n'a point eu de symptomes gastro-intestinaux; La courbe glycémique est normale; l'enfant se développe normalement.

Il n'a pas été possible de prouver non plus qu'il y ait eu apport insuffisant de quelque facteur extrinsèque. La diète a tout le temps été parfaitement appropriée. L'administration de marmite, qui dans les anémies macrocytaires tropiques a un si bon effet, est restée inefficace.

C'est un fait frappant que les rechutes se sont toujours déclarées concurremment avec une maladie infectieuse. Un phénomène qu'il semble qu'on peut également constater dans les cas d'anémie pernicieuse. Et dans le tableau où sont indiqués les examens du sang, on peut voir comment les valeurs hématologiques ont une tendance à décroître aussitôt que le traitement hépatique est suspendu.

Cooley note, comme nous l'avons déjà rapporté, que dans la première enfance peuvent se déclarer, conjointement avec des maladies infectieuses, des anémies qui sont réfractaires au traitement martial comme unique agent thérapeutique, tandis qu'une transfusion de sang ou l'administration d'extrait de foie ont un bon effet. Il est possible que notre cas représente un type d'anémie de ce genre et qu'il se distingue par le fait que cette manière de réagir s'est maintenue pendant un temps prolongé, pour le moment jusqu'à l'âge de trois ans.

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Communication from the Medical Ward of Aalborg Amtssygehus (Denmark).
(Chief: E. Schiodt, M. D.)

# Erythema Nodosum Arising from Treatment With Sulfathiazole.

By

TORBEN JERSILD and KURT IVERSEN.

(Submitted for publication February 20th 1942.)

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During the last year 307 patients have been treated with sulfathiazole (Chemosept) at the hospital. The patients have chiefly been suffering from pneumonia (62 patients) and scarlet fever with complications (58 patients). The rest of the cases include patients with different infectious diseases, medical and surgical. The cases include patients of both sexes of all ages. Peroral medicamentation has principally been used, and only in a very few cases has sulfathiazole been injected.

The doses given are specified in table I:

Table I.

| Age | Number of Patients | Average doses | Largest Total dose | Smallest Total dose |
|---|---|---|---|---|
| 0— 6 months | 9 | 3.5 gr. | 8.3 gr. | 1 gr. |
| 6—12 » | 21 | 5.6 » | 18.5 » | 1.5 » |
| 1— 2 years | 20 | 4.8 » | 11.3 » | 1.5 » |
| 2—14 » | 71 | 11.4 » | 46.0 » | 2.0 » |
| > 14 » | 186 | 22.2 » | 121.0 » | 3.0 » |

It appears from literature that sulfathiazole is just as effective as sulfapyridine but considerably less toxical — an experience we have also learnt, as complications in none of the cases have been of a severe nature, and have always disappeared at once after the discharge of the drug.

Apart from nausea and vomiting, which have only occurred in 6.2 % of the cases and in none of these have been so serious that it was neccessary to discontinue the drug, the most frequent complication has been rashes of different types: morbilliform, scarlatiniform, papular, and often in the form of erythema nodosum, which can neither clinically nor histologically be distinguished from erythema nodosum of tuberculous origin.

Erythema nodosum arising as a result of sulfathiazole treatment has not previously been described in Denmark, whereas similar cases have been reported particularly from America and Switzerland. Perrin H. Long (4) has observed a few cases of erythema nodosum in the course of sulfathiazole therapy, without, however, stating the magnitude or the doses given. Haviland and Long (3) have treated 78 patients with sulfathiazole and erythema nodosum has only been noticed in two cases. Volini, Lewitt and O'Neil (6) have seen rashes in 3.9 % of 180 patients treated with sulfathiazole. Only in three patients the rash appeared as erythema nodosum, and they state, contrary to what we have found, that the morbilliform rash was most frequently seen. Long, Haviland, Edwards and Bliss (5) have treated 271 patients with sulfathiazole. In five per cent of the cases a rash was observed, most frequently in the form of erythema nodosum. In the Scandinavian literature, Frisk (1) has referred two cases of this complication in 17 pneumonia-patients treated with sulfathiazole.

Finally Gsell (2) has found similar skin-eruption in about 8 % of 135 cases treated with Cibazole.

As much literature has already been published regarding sulfathiazole, and as the complications mentioned are only described in comparatively few cases, we are of the opinion that we are justified in reporting briefly the following cases:

***Case I.*** ♀ 18 years. J. No. 875/41.

*Pneumonia:* the patient was treated with sulfathiazole 4+4+2 tablets every 4 hours. The next day the temperature had fallen slightly; later the temperature rose from 38.3 to 39.3 and at the same time — after the pati-

ent had received 20 grams sulfathiazole — erythema nodosum appeared on the forearms and on the anterior surface of the legs. The nodules were from the size of a pea to half-a-crown and were of a bluish-red colour elevated swollen and very tender. No itch and no painful joints.

In spite of the nodules the treatment with sulfathiazole was continued 3 days more (altogether 33 grams sulfathiazole) during which treatment the nodules increased, and, therefore, the drug was stopped. The next day the skin-eruption and tenderness subsided and in the course of three days had quite disappeared. No other complications of any form were observed.

*Examinations:* hemoglobin 90 %. Sedimentation-rate: 117 mm. → 30 mm.
Culture after gastric lavage showed no tubercle bacilli.
Urine: — protein.
Mantoux reaction: — (1/100 mg) + (1/10 mg).
Radiogram of the lungs: normal.

After discharge the patient was examined at the tuberculosis dispensary, but no sign of tuberculosis was found.

***Case II.*** ♂ 11 years. J. No. 1604/41.

*Scarlet fever:* On account of otitis med. dxt. the patient was treated with sulfathiazole, 2 + 1 tablets every 4 hours. 15 ½ grams sulfathiazole was given in the course of 8 days without any complications.

3 days after the discharge of the sulfathiazole a mastoiditis appeared. A resectio partialis proc. mastoid. dxt. was performed and at the same time another treatment with sulfathiazole (2 + 1 tablets every 4 hours) was commenced. The temperature fell gradually. After sulfathiazole was given for 3 days (altogether 6 grams) an erythema nodosum appeared on the anterior surface of the legs without causing a rise of temperature. The sulfathiazole was discharged, and the nodules disappeared in the course of a few days. No nodular eruptions appeared during a subsequent treatment with sulfathiazole 2 weeks later.

*Examinations:* hemoglobin 82 %
white blood cells: 16,400, red blood cells: 4.30 millions
Mantoux: — (1 mg.)
Urine: normal.
Radiogram of the lungs: normal.

*Subsequent examination* 4 months later showed no sign of tuberculosis (Mantoux — 1 mg).

***Case III.*** ♀ 18 years. J. No. 1268/41.

*Scarlet fever:* Sulfathiazole treatment was commenced on account of painful joints and abcessus peritonsillaris. After a dose of 20 grams sulfathiazole was given in the course of 3 days, some bluish-red nodules appeared on the anterior surface of the right forearm and the right leg. The size of the nodules being from a pea to about the size of a shilling. A little albuminuria was found (< 0.1 ‰), but no microscopic hematuria.

The sulfathiazole was stopped and in the course of 2 days the nodules and the albuminuria disappeared. — No other complications were observed.

*Examinations:* Sedimentation-rate: 108 mm → 27 mm/1 hour.
Micr. exam. of the urine: 0
Mantoux: — (1 mg).
Radiogram of the lungs: normal.
Electrocardiogram: normal.

*Subsequent examination* 6 months later: no sign of tuberculosis (Mantoux — 1 mg.)

The following two patients were brother and sister, and were admitted to the hospital on the same day.

***Case IV.*** ♀ 2 years. J. No. 1050/41.

On account of scarlet fever, complicated with sinuitis frontalis et maxillaris dxt. and conjunctivitis purulenta, the patient was treated with sulfathiazole 1 + ½ tablets every 4 hours, after which a gradual fall of temperature occurred. After a dose of 5 ½ grams sulfathiazole, an erythema nodosum eruption appeared symmetrically localized to the anterior surface of the legs. The skin eruption was accompanied by drug-fever. No other complications were observed. The sulfathiazole was stopped the same day, and the nodules disappeared immediately.

*Examinations:* hemoglobin: 105 %
Urine: normal
Micr. exam. of the urine: normal
Mantoux: — (1 mg)

*Subsequent examination* 4 months later: no sign of tuberculosis Mantoux — 1 mg).

***Case V.*** ♂ 3 years. J. No. 1419/41.

*Scarlet fever. — Otitis med. dxt.*

Paracentesis was performed and sulfathiazole was given, 2 + 1 tablets every 4 hours — (altogether 14.5 grams) without any complications.

On account of otitis med. sin. which occurred later, the patient was again treated with sulfathiazole, 2 + 1 tablets every 4 hours. — After a dose of 7 grams had been given, an eruption of erythema nodosum appeared, accompanied by drug fever, on the anterior surface of both legs. The nodules were very red, tender, swollen and of the size of the kernel of a nut.

The treatment was continued during which new nodules still appeared and after the patient had received 15 grams sulfathiazole, the drug was discharged and after this no new nodules were seen. — The nodules disappeared in the course of 3 days.

*Examinations:* hemoglobin 85 %
Sedimentation-rate: 70 mm → 6 mm.
Mantoux: — (1 mg) under several examinations.
Radiogram of the lungs: normal.

The puss from the ear. — tubercle bacilli by culture.

*Subsequent examination* 4 months later: no sign of tuberculosis. (Mantoux — 1 mg.)

**Case VI.** ♂ 11 years. J. No. 1244/41.

The patient was admitted to the surgical ward, suffering from *vulnus contusum et dilaceratum cruris* and was among other things treated with sulfathiazole, altogether 22 grams without complications.

Later on admitted to the medical ward, suffering from *scarlet fever.* The patient was very feverish and intoxicated, and therefore serum against scarlatina (40 $cm^3$) was given. As the temperature was not affected by this, a further dose of sulfathiazole, 1 tablet × 4 daily, was given (altogether 12 grams) without any complications.

On account of renewed fever, treatment with sulfathiazole was again begun 14 days later (2 tablets × 4 daily).

3 days later after a dose of 12 grams sulfathiazole had been administered in this series, an erythema nodosum eruption appeared, without a rise of temperature. The skin eruption consisted of many tender nodules, localized to the anterior surface of both legs and forearms.

The sulfathiazole was discharged and 2 days later the eruptions disappeared.

*Examinations:* hemoglobin 80 %.
Blood-count: normal.
Mantoux: — (1 mg.)
Urine: normal.
Radiogram of the lungs: normal.

*Subsequent examination* 4 months later: no sign of tuberculosis (Mantoux — 1 mg).

**Case VII.** ♀ 68 years. J. No. 637/41.

*Broncho-pneumonia.* Was treated with sulfathiazole, 4 + 4 + 2 tablets every 4 hours. After a dose of 24 ½ grams sulfathiazole, some red, tender, swollen nodules of the size of a half-penny appeared in the deeper layers of the skin and subcutis on the anterior surface of the legs. At the same time an intense scleral injection appeared on the left eye.

The sulfathiazole was stopped and the erythema nodosum and the scleral injection disappeared in the course of a few days.

*Examinations:* hemoglobin 110 %.
Sedimentation-rate: 44 mm.
Wassermann reaction: negative.
Micr. exam. of urine: normal.
Mantoux: + (1/100 mg.).
Sputum: — tubercle bacilli by culture.

The patient was later on admitted to the surgical department suffering from ileus.

*Subsequent examination* 8 months later: no sign of tuberculosis.

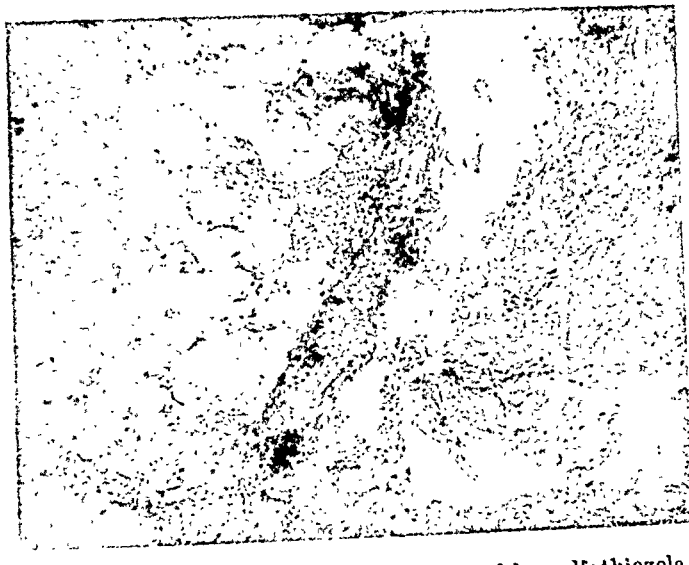
***Case VIII.*** ♀ 27 years. J. No. 1841/41.

*Panaritium.* — which was lanced.

On account of fever sulfathiazole was administered (4 + 2 tablets every 4 hours). After a dose of 15 grams, an erythema nodosum eruption occurred on both knees and on the anterior surface of the left forearm. The nodules were about the size of a half-penny, tender and not confluent.

The eruption quite disappeared in the course of 2 days after stopping the drug.

*Examinations:* Sedimentation-rate: 6 mm.
Mantoux: + (1/10 mg.)
Radiogram of the lungs: normal.
Culture after gastric lavage showed no tubercle bacilli.



Microphotograph of erythema nodosum, caused by sulfathiazole (case 9).

***Case IX.*** ♂ 19 years. J. No. 1798/41.

*Appendicitis acuta. Bronchopneumonia.*

A bronchopneumonia occurred as a complication to an acute appendicitis and, therefore, sulfathiazole was administered, altogether 47 grams in the course of 9 days. After this an erythema nodosum eruption appeared on the anterior surface of the legs and a single nodule of about the size of a shilling on the right forearm. — The nodules were red, bluish, from the size of a sixpence to a shilling, partly swollen and very infiltrated and tender. On the anterior surface of the right leg the nodules were partly confluent.

At the onset of the skin-eruption the patient had severe pain in his right knee, and complained much even at the least movement.

The joint was swollen, but no exudate was found.

The sulfathiazole was stopped and next day the pain in the knee had disappeared and he could move his leg actively. Already the next day the



Erythema nodosum arising from treatment with sulfathiazole (case 9).



Erythema nodosum arising from treatment with sulfathiazloe (case 9).

skin-eruption had subsided and was much paler and in some places more confluent (see photo).

The onset of this eruption was accompanied by drug fever (39.4). When stopping the drug the temperature fell immediately to 36.8 and remained normal. In the course of 2 days the skin-eruption had absolutely disappeared.

*Examinations:* Sedimentation-rate: 42 mm —> 10 mm.
Micr. exam. of urine: normal.
Mantoux: — (1 mg.)
Radiogram of the lungs: normal.
Sputum: — tubercle bacilli.
Culture after gastric lavage showed no tubercle bacilli.

*Histological examination*

of an erythema nodosum element:

Epidermis is thin and normal and a few leucocytes are found here. Hair, sebaceous glands, and sweat glands are normal. Definite changes are found in the connective tissue; the changes are sligthly visible in the corium but become more accentuated on the border of the corium-subcutis and in the subcutis. Here one finds inflammations, mainly localized around the blood-vessels. In the corium only a few infiltrations of leucocytes and plasma-cells around the capillaries are to be seen. These increase in the deeper layers, and on the border of the subcutis one finds massive infiltrations of leucocytes, plasma-cells and lymfocytes, partly diffused in the fat and the connective tissue, but chiefly around the vessels, which in many places show necrosis of the vascular wall, proliferation of the endothelium and occlusion of the lumina. In the tissue scattered hemorrhages are to be found.

No sign of specific inflammation, nor of tumors is to be found. Edema is only seen in a small degree and hyaline transformation of the small vascular walls have not been observed (see microphoto). — — The histological examination corresponds to what is described as erythema nodosum.

(Professor Engelbreth-Holm, Copenhagen).

*Epicrisis.*

During treatment with sulfathiazole erythema nodosum eruption appeared in 9 patients, chiefly localized to the anterior surface of the legs.

The skin-eruption appeared in 5 of the cases (cases 1, 3, 4, 7, 8) on the third or fourth day of treatment after a total dose of 16 grams of sulfathiazole.

In 3 of the cases (cases 2, 5, 6) sulfathiazole had been given (in average doses of 16 grams) in one or two preceding series of treatment — without any complications. Under a renewed treatment the skin eruption appeared on the third day of treatment — after an average dose of 8 ⅓ grams had been given.

In one case (case 9) the skin-eruption did not appear before the ninth day — after a total dose of 47 grams sulfathiazole. Only in this case the skin-eruption was accompanied by painful affection of the joints, which disappeared at the same time as the drug had been stopped.

All the patients were thoroughly examined for an eventual tuberculous infection, but in none there was any sign of tuberculosis.

The erythema nodosum caused by sulfathiazole treatment could neither clinically nor histologically be differentiated from that of tuberculous origin.

The point that should be emphasized is that these erythema nodosum eruptions after sulfathiazole treatment disappeared much sooner than those of tuberculous origin (namely 2—3 days after the drug was discontinued).

*Other toxic complications of sulfathiazole.*

During the treatment of the 307 patients with sulfathiazole we have not observed any cases of hepatitis, icterus nor blood-changes, as severe anemia, leucopenia or agranulocytosis. Neither dizziness nor psychosis were seen. In only a few cases have we observed cyanosis, which often occurs during sulfapyridine treatment. Hematuria occurred only in a single case, and a slight and transient albuminuria had been noticed in 3 cases.

To simplify matters all the complications are placed in the following table II.

Table II.

*Manifestations of Sulfathiazole Toxicity in 307 Patients.*

| | |
|---|---|
| Nausea | 2.3 % |
| Nausea, vomiting | 6.2 % |
| Hematuria | 0.3 % |
| Albuminuria | 1.0 % |
| Drug fever | 1.6 % |
| Neuritis | 0.3 % |
| Injection of scleras and conjunctivas | 1.3 % |
| Rash | 4.9 % |
| » scarlatiniform and morbilliform | 1.0 % |
| » papular | 1.0 % |
| » Erythema nodosum | 2.9 % |
| Painful joints | 0.3 % |

## Summary and conclusion.

307 patients, of all ages and of both sexes, have been treated with sulfathiazole. The average dose has varied from 3.5 grams (infants) to 22.2 grams (adults). The following complications have been observed: vomiting in 6.2 %, rashes in 4.9 %, often in the form of erythema nodosum which neither clinically nor histologically could be differentiated from that of tuberculous origin. In none of these 9 patients was there any sign of tuberculosis. In addition we have noted: drug fever in 1.6 %, hematuria in 0.3 %, scleral injection in 1.3 %, but on the other hand leucopenia, severe anemia and agranulocytosis have not been observed at all.

In none of the cases have the complications mentioned been of a serious nature, and the point should be emphasized, that all the complications disappeared immediately when the drug was stopped. In 3 cases the complications did not occur again although a new series was given.

### Literature.

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# Experimental studies on production of pernicious anemia by operation on the digestive tract.[1]

## 5. Results of Extensive Resection of the Proximal Part of the Small Intestine (on Pups).

By

SVEND PETRI, HANS JENSENIUS, FLEMMING NØRGAARD and ERIK THYSSEN.

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## Introduction.

Experimental resection of 60—80 % of the *distal* part of the small intestine on pups has constantly resulted in a pellagrous fatal symptom complex resembling pernicious anemia, sprue and, in particular, the special form of terminal ileitis described by Plum & Warburg (Petri, Jensenius, Nørgaard & Thyssen, Acta med. Scand. 1942). This observation made it desirable through systematic experimentation to try to elucidate the causal significance of the small intestine to the development of the lesions mentioned.

For this purpose, several experimental series have been commenced with different extensive operations performed on the same distal or proximal parts of the small intestine (simple resection, transformation of the intestinal section into an intestinal fistula,

[1] These studies were carried out with the aid of a grant from P. Carl Petersen's Fond and by private means.
Translated from Danish by Hans Andersen, M. D., Copenhagen.

»short-circuiting» by side-to-side anastomosis, or by diverticulum formation by end-to-side anastomosis) with or without subsequent varying therapy.

The experiments with proximal resection of the small intestine reported in the following, together with the above-mentioned experiments with distal resection of the small intestine, represent the first of the operation groups named above.

## Material and Experimental Conditions.

Two pups, 5 months old: No. 111, male; 5.53 kg, 62 cm; and No. 110, male; 6.95 kg, 66 cm.

By resection of the small intestine 150 cm (No. 111) and 180 cm (No. 110), from the jejunal flexure of the duodenum, were removed; these sections were measured immediately after their removal. On autopsy there remained respectively 49 cm and 38 cm of small intestine, measured from the site of the anastomosis to the ileocecal junction — *i. e.*, the resection has involved respectively the *proximal 75 % and 82 % of the small intestine.* The anastomosis was made side-to-side.

Observation period: 299 days (No. 111) and 300 days (No. 110).

The general experimental conditions have been the same as in the previous experiments.

## Clinical and Morphological Changes in the Animals.

***Experiment 1.*** (Pup No. 111; observation period 299 days.)

The animal was normal as to behavior, appetite and defecation. For a while the increase in weight seemed to be checked a little, and the nutrition appeared to vary slightly. A few bare spots appeared on the head (on the 44th day), and the hair was thinning out slightly on the extremities (91th day). During the next 3 months the loss of hair was increasing slightly in degree and extension; at the same time, the animal appeared to be ailing a little. On all four legs, on the anterior surface, near the body, there appeared a sharplyd efined hairless area with thickening of the skin (145th day). No pigmentation of the skin. No clinical signs of any affection of the central nervous system. The skin changes subsided gradually in the course of a couple of months. When the animal was killed (7/8 40) its appearance was perfectly normal. Marked hypoacidity was ascertained about the 48th and 93th days. There were practically no

**Table 1.**

*Dog No. 111.*

| Date | Hb % | Red blood cells in millions | White blood cells | Color index | Volume % | Reticulocytes ‰ | Diameter of red blood cells | | | Size of animal | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Minimum μ | Maximum μ | Average μ | Length cm | Weight kg |
| 11/10 39 | 77 | 5.39 | 22,080 | 0.71 | 40 | 6 | 6.0 | 8.0 | 7.09 | 62 | 5,530 |
| 13/10 » | Operation | | | | | | | | | | |
| 25/11 » | 77 | 5.63 | 20,960 | 0.68 | 38 | 13 | 5.5 | 8.5 | 6.93 | 62 | 5,980 |
| 28/12 » | 68 | 4.98 | 39,120 | 0.68 | 32 | 6 | 5.5 | 8.0 | 6.86 | 63 | 6,450 |
| 1/ 2 40 | 73 | 5.11 | 26,120 | 0.60 | 34 | 4 | 6.0 | 7.5 | 6.78 | 63 | 8,320 |
| 28/ 2 » | 71 | 6.41 | 30,840 | 0.56 | 39 | 4 | 6.0 | 8.5 | 7.24 | 65 | 7,750 |
| 28/ 3 » | 68 | 5.69 | 24,200 | 0.60 | 41 | 4 | 5.5 | 8.0 | 6.78 | | 6,830 |
| 30/ 4 » | 80 | 6.09 | 23,680 | 0.66 | 40 | 26 | 6.0 | 8.0 | 7.13 | | 7,400 |
| 8/ 5 » | 78 | 7.27 | 33,680 | 0.54 | 36 | 11 | 6.0 | 8.0 | 6.90 | | |
| 30/ 5 » | 76 | 6.78 | 28,680 | 0.56 | 33 | 12 | 6.0 | 8.5 | 7.07 | | |
| 26/ 6 » | 76 | 6.59 | 20,160 | 0.58 | 39 | 6 | 6.0 | 8.0 | 6.91 | | |
| 26/ 7 » | 84 | 7.15 | 19,800 | 0.59 | 43 | 11 | 5.5 | 8.0 | 6.90 | | |
| 7/ 8 » | Died | | | | | | | | | | |

changes in the hemoglobin percentage. Moderate increase in the red blood count (from 5.39 million to 7.27 million) beginning about 4 ½ months after the operation; a suggestion of macrocytosis.

Blood examination, test-meals, measurements and weights recorded in Tables 1 and 3.

*Morphological Changes. — Macroscopic findings:* Peritoneum appearing normal except for a few fibrillary adhesions. Anastomosis looking natural. Measure of the small intestine from the pylorus to the site of the anastomosis, 24 cm (= the entire duodenum); from this site to the ileocecal junction, 49 cm. Mucous membrane of the digestive canal appearing normal. Other organs normal.

*Microscopic examination:* Bone marrow of vertebral bodies containing relatively scanty fat-cells; normal structures of the cellular marrow. Femur: Some areas containing many fat-cells, other areas but few. Tibia: Fatty marrow, free from cells.

Central nervous system: No definite abnormality, merely some doubtful changes in the Purkinje cells.

Lymph glands: Slight hemosiderosis; some plasma cells. Testes: Normal spermatogenesis. Skin: Remnants of hyperkeratosis. Intestinal mucosa: Some round cell infiltration; in the vicinity of the ileocecal junction, numerous rather larger lymph follicles and a few small disseminated infiltrations with leucocytes and plasma cells. Other organs: No changes.

**Table 2.**

*Dog No. 110.*

| Date | Hb % | Red blood cells in millions | White blood cells | Color index | Volume % | Reticulocytes ‰ | Diameter of red blood cells | | | Size of animal | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Minimum μ | Maximum μ | Average μ | Length cm | Weight kg |
| 11/10 39 | 84 | 5.19 | 13,000 | 0.81 | 37 | 7 | 5.5 | 8.0 | 6.85 | 66 | 6,950 |
| 12/10 » | Operation | | | | | | | | | | |
| 25/11 » | 93 | 6.38 | 11,360 | 0.73 | 41 | 9 | 5.5 | 8.5 | 7.10 | 67 | 7,715 |
| 28/12 » | 88 | 5.82 | 9,040 | 0.76 | 42 | 3 | 6.0 | 8.0 | 6.88 | 67 | 9,500 |
| 1/ 2 40 | 93 | 6.52 | 17,760 | 0.71 | 42 | 6 | 5.5 | 8.0 | 7.01 | 68 | 9,590 |
| 28/ 2 » | 84 | 6.47 | 14,160 | 0.65 | 44 | 5 | 6.0 | 8.0 | 7.01 | 69 | 10,005 |
| 28/ 3 » | 100 | 6.53 | 12,560 | 0.77 | 47 | 4 | 6.0 | 8.5 | 7.37 | 69 | 11,000 |
| 30/ 4 » | 102 | 7.53 | 10,240 | 0.68 | 42 | 16 | 6.0 | 8.5 | 7.12 | | |
| 8/ 5 » | 104 | 7.17 | 11,440 | 0.73 | 49 | 7 | 6.0 | 8.5 | 7.05 | | |
| 30/ 5 » | 104 | 6.86 | 8,040 | 0.76 | 49 | 7 | 6.0 | 9.0 | 7.45 | | |
| 26/ 6 » | 106 | 7.38 | 9,160 | 0.72 | 50 | 4 | 6.0 | 8.5 | 7.25 | | |
| 26/ 7 » | 100 | 6.55 | 10,440 | 0.76 | 49 | 5 | 6.5 | 8.5 | 7.47 | | |
| 7/ 8 » | Died | | | | | | | | | | |

***Experiment 2.*** (Pup No. 110; observation period 300 days.)

Throughout the observation period the animal was normal as to behavior, weight, nutrition, appetite and defecation. A few bare spots appeared on the head and both hind legs (68th day) and a little later on the trunk too. A bare area with thickening of the skin was noticed (159th day) together with redness and small postules. The skin changes disappeared gradually within a couple of months. When the animal was killed (7/8 40), its appearance was perfectly normal. Within a period of 4 months (from 56th to 175th days): Alternating hypoacidity and achylia. The hemoglobin percentage was rising gradually (from 84 to 106); there was a rather early and persistent increase in the red blood count (from 5.19 to 7.53 million). Pronounced macrocytosis.

Blood examination, test-meals, measurements and weights recorded in Tables 2 and 3.

*Morphological Changes. — Macroscopic findings:* Peritoneum appearing normal except for some fibrillary adhesions here and there. Measure of the small intestine from the *pylorus* to the anastomosis, 23 cm (= the entire duodenum); herefrom to the ileocecal junction, 38 cm. Mucous membrane of the digestive canal appearing normal. Other organs normal.

*Microscopic examination:* Bone marrow of vertebral bodies containing a moderate amount of fat-cells; normal structures of the cellular marrow. Femur: Some areas containing many fat-cells, other areas but few. Tibia: Fatty marrow, free from cells.

**Table 3.**

*Test meals.*

| Dog No. 111 | | | | Dog No. 110 | | | |
|---|---|---|---|---|---|---|---|
| Date | Amount | Congo | Phenolph-thalein | Date | Amount | Congo | Phenolph-thalein |
| 11/10 39 | 40 | 32 | 45 | 11/10 39 | 10 | 10 | 25 |
| 27/10 » | ca. 1 | + | | 27/10 » | 7 | (+) | 48 |
| 2/11 » | 9 | 21 | 54 | 2/11 » | 14 | 31 | 59 |
| 9/11 » | 25 | 39 | 83 | 9/11 » | 80 | 47 | 68 |
| 16/11 » | 110 | 28 | 110 | 16/11 » | 40 | 40 | 98 |
| 27/11 » | 21 | 8 | 26 | 5/12 » | 30 | 0 | 3 |
| 5/12 » | 38 | 31 | 46 | 11/12 » | 25 | 12 | 19 |
| 11/12 » | 25 | 26 | 41 | 21/12 » | few drops | + | |
| 29/12 » | 20 | 65 | 75 | 11/ 1 40 | 5 | 0 | 10 |
| 11/ 1 40 | 10 | 3 | 25 | 25/ 1 » | 38 | 22 | 33 |
| 25/ 1 » | 5 | 22 | 30 | 12/ 2 » | 2 | 0 | 10 |
| 12/ 2 » | 15 | 36 | 44 | 5/ 3 » | 75 | 10 | 80 |
| 5/ 3 » | 11 | 34 | 43 | 2/4 » | 21 | 13 | 20 |
| 2/ 4 » | 25 | 46 | 62 | 23/ 4 » | 19 | 32 | 63 |
| 23/ 4 » | 17 | 39 | 54 | 10/ 5 » | 10 | 51 | 60 |
| 10/ 5 » | 30 | 41 | 58 | 20/ 6 » | 30 | 45 | 56 |
| 20/ 6 » | 16 | 53 | 65 | 7/ 8 » | 50 | 44 | 63 |
| 6/ 8 » | 18 | 45 | 56 | | | | |

Central nervous system: Spinal cord, no definite abnormality. Medulla oblongata, pons and corpora quadrigemina: Scattered sclerotic cells, in part with glia reaction; in addition, the corpora quadrigemina show a few moderately swollen cells within a group of large motor ganglion cells. Cerebellum: Here and there some moderately swollen cells and a few shrunken cells among the normal Purkinje cells. Basal ganglia: A few scattered sclerotis cells. Cerebral cortex: No abnormality.

Liver: A minority of the liver cells are fat-containing; scanty periportal round-cell infiltration. Spleen: Very pronounced hemosiderosis; slight fibrosis (?). Testes, skin and intestine: Same findings as in No. 111 (but no infiltrations in the intestinal mucosa). Other organs: No changes.

## Recapitulation.

Resection of the *proximal 75—82* % of the small intestine in 2 pups produced clinically a slight transitory loss of hair and hypoacidity or achylia. In addition, there developed a persistent normochromic, respectively hypochromic, polycytemia (maximum

2½ million over the initial values) with a suggestion, respectively a more pronounced degree, of macrocytosis. The presumably slightly hyperplastic bone marrow showed normal morphological structure. In one of the animals the spleen showed marked hemosiderosis, and the central nervous system presented slight or moderate, mostly chronic, degenerative changes in the ganglion cells (most pronounced in the brain stem). The animals did not die spontaneously.

The lesion may be characterized as a slight, chronic, partly remittent subpellagra with transitory lowering of the stomach function, besides polycytemia and a tendency to macrocytosis.

## Comments.

According to our previous resection experiments, removal of less than the distal 80 % of the small intestine produces constantly a fatal subacute or chronic pellagrous affection (»enterogenous» pellagra) accompanied by hyperchromic macrocytic anemia, chronic diarrhea and a tendency to achylia (cf. Introduction). Thus there is a pronounced difference in the character, degree and clinical course between this syndrome and the morbid condition observed after resection of the proximal part of the small intestine.

The two groups of resection experiments appear to have established the significance of the *ileum* to the development of »enterogenous» pellagra, hyperchromic (macrocytic) anemia, chronic diarhhea and possibly achylia (»enterogenous» = ileoprival), and, on the other hand, the significance of the *jejunum* to the production of a polycytemic blood reaction.

As a fairly large middle section of the small intestine was removed in both types of resection, according to the difference in the clinical features it seems reasonable then to expect that a less extensive proximal resection might result merely in polycytemia.

In previous papers we have discussed the cause of the »enterogenous» (= ileoprival) pellagra and the particular concomitant changes (the special type of anemia and the diarrhea). The present experiments offer merely a contribution to the elucidation of the pathogenesis of the diarrhea. From resection of the proximal part of the small intestine it thus is evident that *neither removal of a large section of the small intestine itself nor lowering of the stom-*

*ach function gives rise to chronic diarrhea.* The interest, therefore, centers around the possibility that the ileum, perhaps even only the distal 20 % of this section of the gut, might be associated with a specific — presumably absorptive — function, preventive of diarrhea. Attemps are now being made to elucidate this question by means of absorption experiments on jejunum-or ileum-resected pups (Jensenius).

## Summary.

A report is given of the results from resection of 75—82 % of the *proximal* part of the small intestine on two pups, with an observation period of 299 and 300 days, respectively.

The operation brought about the development of a slight, chronic, partly remittent subpellagra with transitory lowering of the stomach function, together with polycytemia and a tendency to macrocytosis.

This clinical picture differs markedly from the one observed by us before, after extensive resection of the *distal* part of the small intestine [fatal, subacute or chronic »enterogenous» pellagra + tendency to achylia + hyperchromic (macrocytic) anemia + chronic diarrhea].

The *ileum* thus appears to be that section of the small intestine which is decisive of the development of »enterogenous» pellagra (+ special changes), whereas the jejunum appears to be of specific significance to the production of a polycytemic blood reaction.

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# Parotitis Meningitis with Special Reference to Cases Without Swelling of the Parotid Gland.

## Epidemic in the County of Aalborg.

By

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Meningitis is generally regarded as a rather rare complication of epidemic parotitis. However, of late years a number of cases of this complication have been reported from various countries, particularly from France.

In Denmark Krabbe (4) has reported a case of serous meningitis, possibly induced by the mumps virus; and further we have more recent reports by Schiødt (10), Nissen (7) and Kofoed (3).

The meningitis may develop both before, simultaneously with, and after the parotitis; but in the literature we find but few reports of cases in which meningitis is the only symptom of the mumps infection. In Scandinavia Wallgren (12) has reported two cases of mumps meningitis in which the patients lived in parotitis surroundings without having or having had parotitis. Similar isolated cases have also been reported by Ask-Upmark (1), Morquio (6), Schoerder (9), Paddock (8) Silwer (11) and Linde (5).[1] In Denmark Johansen (2) has published 5 cases of mumps meningitis. In one case the patient presented no symptoms of mumps, whereas there was found parotitis in the other patients.

[1] After the completion of this article G. Ahlberg has published in Nord. med. Tidsskr. 1942: *13:* 206, 2 cases of mumps meningitis without swelling of the parotid gland.

During an parotitis epidemic we treated in the Aalborg Amtssygehus (county hospital) 7 cases of mumps meningitis accompanied by parotitis, and 11 cases of serous meningitis without swelling of the parotid gland, but in which cases the epidemiological circumstances and the course of the disease were greatly in favour of the same etiology.

Hitherto only sporadic cases of mumps meningitis without swelling of the parotid gland have been described, accordingly I shall here give an account of this epidemic manifestation of the disease. But first I shall briefly mention the case records in which the meningitis was accompanied by parotitis.

*In the following 7 cases the meningitis was accompanied by parotitis:*

***Case I.***

(No. 162/42). ♂ aged 11. Admitted on Jan. 13, 1942.

Has not previously had parotitis. About half of the patient's classmates have mumps. 7 days before entry he had fallen ill with fever and swelling of both parotid glands. 3 days before entry, when the swelling had almost disappeared, and the temperature had been normal for about 48 hours, his temperature rose again (39.6° C, 103, 3° F), he had headache and violent fits of vomiting, and he was not quite conscious.

*Jan. 13, on entry:* Temperature 38.9° C (102° F). The patient was somewhat absent, his face was flushed with a circumoral paleness. No swelling of the parotid glands. Marked stiffness of the neck, and Kernig's test highly positive. *The spinal fluid* was rather clear, 3104/3 cells (chiefly lymphocytes). Pandy's test positive, 15 alb., 1 glob., W. R. in the spinal fluid: negative, culture: no growth, no T. b. The temperature fell lytically and was normal on Jan. 16 (6 days after the onset of the meningitis).

Jan. 17: No stiffness of the neck. Kernig negative.

Jan. 27: Feeling perfectly well. — Discharged.

In this case the diagnosis presented no difficulties. The meningitis developed 4 days after the parotitis, and the meningeal symptoms vanished in the course of 6 days.

***Case II.***

(No. 1545/41). ♂ aged 14. Admitted on Sept. 1, 1941.

Has not previously had parotitis. Fell ill 2 days before entry with fever (39.5° C, 103.1° F), vomiting and headache, lying mostly in a doze, but not delirious. On his admittance to hospital there was marked stiffness of the neck with positive Kernig. His face was flushed with a pronounced circumoral paleness. Temperature 39.9° C (103.8° F). No swelling of the parotid glands. Spinal fluid rather clear, 1410/3 cells (lymphocytes). Pandy positive, 10 alb., and 0 glob., no bacteria, no growth, no T. b. in culture.

Was treated with sulfathiazole (altogether 15 grams). The day after his admittance there was found swelling and tenderness of the left parotid gland.

Sept: 5: The headache has disappeared, only inconsiderable stiffness of the neck.

The temperature fell lytically and was normal on Sept. 7.

Sept. 22: Kernig negative. Sept. 27: Discharged.

In this case the meningitis developed previous to the parotitis, which did not appear till 3 days after the onset of the meningitis.

***Case III.***

(No. 2/42), ♀ aged 9. Admitted on Jan. 1, 1942.

4 weeks before entry the patient had mumps. On the day of entry she suddenly fell ill with headache, vomiting, and convulsions. Temperature on entry 38.5° C (101.3° F). She was absent, but not delirious. Kernig positive.

The temperature fell lytically and became normal within 8 days.

Jan. 12: *Spinal fluid* clear, 268/3 cells (lymphocytes), 30 alb. and 1 glob.

Jan. 27: 49/3 cells, Pandy negative. W. R. negative, no bacteria, no growth, no T. b.

In this patient the meningitis appeared 4 weeks after the parotitis. The interval is here unusually long. Yet Morquio has described a case in which the meningitis developed 2 months after the parotitis.

***Case IV.***

(No. 2207/41). ♂ aged 38. Admitted on Dec. 18, 1941.

*Diagnosis:* epidemic parotitis, orchitis, *serous meningitis.* 6 days before entry the patient fell ill with swelling, pains, and tenderness of both parotid glands. The following day pains and tenderness of the left testis.

Dec. 16 (2 days before entry): Exacerbation with headache and vomiting. The patient became lucifugal and there was stiffness of the neck.

*Dec. 18, on entry:* Temperature 39.9° C (103.8° F). Moderate swelling of both parotid glands. Feeling great pain, apathetic and dozing. Marked stiffness of the neck with positive Kernig and Brudzinski. The *l.* testis almost the size of a hen's egg, tender.

Dec. 19: *Spinal fluid* clear, 867/3 cells, mononuclear, no bacteria, no growth, W. R. negative.

Dec. 21: (4 days after entry): Normal temperature.

Dec. 26: No stiffness of the neck. Kernig negative. Dec. 29: Discharged.

This patient developed a left-sided orchitis the day after the onset of the parotitis, and 4 days later the meningitis appeared.

***Case V.***

(No. 1867/41). ♂ aged 22. Admitted on Oct. 26, 1941.

*Diagnosis:* epidemic parotitis, serous meningitis, orchitis.

2 days before entry the patient developed a dextral parotitis, and the following day severe headache and numerous fits of vomiting.

*Oct. 26, on entry:* Temperature 39.4° C (103° F). Is somewhat apathetic, but not exactly reduced. Some swelling of the *r* parotid gland. Marked stiffness of the neck, Kernig and Brudzinski positive. *Spinal fluid* clear 1000/3 cells, Pandy positive, *growth of gram-negative rod-bacteria, which cannot be identified with the usual pathogenic bacteria.* No T. b. in culture. Mantoux: — (1 mg.). W. R. negative.

The temperature fell lytically during the first 4 days.

Oct. 30: Swelling of the *l.* testis. An increase in temperature from 38.4° C (101.1° F) to 40.3° C (104.5° F).

Nov. 3: The temperature is normal and has remained normal since.

In this case the meningitis developed the day after the onset of the parotitis, and the orchitis 6 days later.

***Case VI.***

(No. 291/42). ♀ aged 24. Admitted on Febr. 8, 1942.

*Diagnosis:* epidemic parotitis, serous meningitis.

Previously well, except for scarlatina.

The day before entry headache, swelling and tenderness of the *l.* parotid gland, and temperature about 39° C (102.2° F).

*Febr. 8, on entry:* Temperature 39.9° C (102.7° F), pulse 84, The patient is not reduced. Inconsiderable stiffness of the neck, Kernig and Brudzinski negative. Considerable swelling and tenderness of the *l.* parotid gland, only slight swelling of the *r* one.

*Spinal fluid:* clear, 276/3 cells, mononuclear. Pandy positive, 10 alb., 1 glob., no bacteria, no growth, no T. b. W. R. negative. The temperature ell lytically and was normal 8 days after the admittance to hospital.

There have been numerous cases of mumps in the patient's surroundings. The parotitis and the meningitis developed simultaneously.

***Case VII.***

(No. 316/42). ♀ aged 17. Admitted on Febr. 11, 1942 for pneumonia. Previously well, has not had mumps.

One week before entry tenderness but no swelling of the parotid glands. A few days later (Febr. 7) she fell ill with intense headache, numerous fits of vomiting, and temperature about 40° C (104° F). No coughing nor expectoration.

*Febr. 11, on entry:* Temperature 39.3° C (102.7° F), pulse 76. Is somewhat restless, but not reduced, perspiring with circumoral paleness. Steth. pulm.: nothing abnormal.

Marked stiffness of the neck. Kernig and Brudzinski positive. No swelling nor tenderness of the parotid glands.

*Spinal fluid:* opalescent, 1532/3 cells, mononuclear, no bacteria, no T. b., W. R. negative, Pandy positive, 10 alb., 1 glob.

The temperature fell lytically.

Febr. 15: Temperature normal, no clinical symptoms of meningitis.

Several cases of mumps in the neighbourhood. On the farm where the patient is in service a boy had parotitis 3 weeks before the onset of her disease. The tenderness that was present before her admittance to hospital is suggestive of a slight attack of parotitis preceding the meningitis, although, indeed, there was no swelling of the parotid glands. Thus this is a transition case between the cases of meningitis with a marked swelling of the parotid gland and those in which no parotitis could be demonstrated clinically.

*In the following 11 patients a serous meningitis was demonstrated, but there was no swelling and not even tenderness of the parotid glands.*

***Case VIII.***

(No. 848/41). ♂ aged 2. Admitted on May 9, 1941.

Previously well, has not had parotitis.

Has been feeling bad for a few days before entry, poor appetite, headache, and some vomiting. Has been lying with his head bent backwards. A few convulsive attacks immediately before entry.

*May 9, on entry* Temperature 39° C (102.2° F), pulse 136, somewhat absent and dozing. Cries a good deal and is irritable when touched. Inconsiderable stiffness of the neck. Brudzinski (positive), Kernig (positive). No swelling of the parotid glands. Fauces: some redness and moderate swelling.

*Spinal fluid:* slightly opalescent, 1800/3 cells (mononuclear), no bacteria, no T. B. in culture.

The first day after his admittance he had three convulsive attacks. The convulsions were bilateral, and they were attended by involuntary discharge of urine. The attacks were followed by slight grating of the teeth. Treated with sulfathiazole (altogether 17.5 grams).

The temperature fell lytically in the course of 6 days and has been normal since May 15.

May 18: Still very irritable, crying. There is slight stiffness of the neck.

May 20: Feeling perfectly well. Kernig negative.

May 21: Discharged.

This patient coming from Aalborg city was the first to be admitted with serous meningitis without swelling of the parotid gland, and he was admitted several months before the actual mumps epi-

demic in the county of Aalborg, for which reason nobody thought of connecting the meningitis with the mumps virus. But later when the material was examined, this case was included in the examinations, and there proved to have been a number of cases of parotitis in the immediate surroundings of the child. 3 weeks before the patient was admitted the servant had had parotitis. A few days after his admittance his brother was affected with mumps, and the day before his discharge also his mother developed parotitis. The parents had been greatly astonished that the boy, who returned to these parotitis surroundings, was not affected. All these circumstances considered there is no doubt that in this case the meningitis must have been the only manifestation of epidemic parotitis.

The following 10 patients with serous meningitis without swelling of the parotid gland were admitted within the period from Nov. 1941 till Febr. 1942. During the same period the mumps epidemic in the County of Aalborg reached its climax.

***Case IX.***

(No. 15/42). ♀ aged 11. Admitted on Jan. 2, 1942.

Has not previously had parotitis.

The day before entry she suddenly fell ill with temperature of 39.3° C (102.7° F), headache, and numerous fits of vomiting. Immediately before entry the patient had convulsions in hands and feet with typical tetany attitude.

*Jan. 2, on entry:* The patient is reduced; her pulse is hardly perceptible. Her hands are kept in a typical tetany attitude. Inconsiderable stiffness of the neck, Kernig and Brudzinski positive. The tetany being regarded as gastrogenic the patient was treated with salt-water and glucalcin i. v., after which she improved considerably. No convulsive attacks since.

*Spinal fluid:* slightly opalescent, 1496/3 cells, mononuclear, 10 alb., 1 glob.

Jan. 10: 1295/3 cells. Jan. 26: 142/3 cells, Kernig positive. *Culture: Pure culture of gram-negative rods, which do not ferment away any kind of sugar, and which cannot be identified with any well-known pathogenic bacteria.*

No T. b. in culture. W. R. negative.

The temperature fell lytically and was normal after 6 days.

The majority of her class-mates have parotitis. On the day of her admittance to hospital her brother fell ill with mumps, with considerable swelling of the left parotid gland.

***Case X.***

(No. 1918/41). ♂ 3 years and 6 months old. Admitted on Nov. 6, 1941. Has not previously had parotitis. Many cases of parotitis in the neighbour-

hood. 4 days before entry he was tired, not feeling well, his appetite was poor, he had numerous fits of vomiting. Complained of »toothache».

Nov. 4: Several fits of screaming, put his hands to his head. Temperature 39° C (102.2° F). There was never swelling of the parotid glands.

*Nov. 6, on entry:* Temperature 39.2° C (102.6° F), pulse 120. Is apathetic and quite uninterested. Marked stiffness of the neck, Brudzinski (positive), Kernig positive. Circumoral paleness. Is lucifugal. Fauces: redness and swelling.

*Spinal fluid:* clear, 1200/3 cells. Pandy negative. No bacteria, no growth, no T. b. in culture.

Nov. 8: stiffness of the neck. Kernig positive.

The temperature fell lytically, since Nov. 11 normal (about 7 days after the onset of the disease).

Nov. 10: No meningeal symptoms. Nov. 20: Discharged.

Later I was informed that his brothers and sisters developed mumps 8 days after his return, and his parents were astonished that he did not get the disease.

***Case XI.***

(No. 2070/41). ♂ aged 6. Admitted on Nov. 21, 1941.

Previously always well. Has not had parotitis. Many cases of mumps in the neighbourhood.

The day before entry he felt rather bad, complained of intense headache. Temperature 38,2° C (100.8° F), in the evening 39.6° C (103.3° F).

In the course of the night many fits of vomiting.

*Nov. 21, on entry:* Temperature 38.8° C (101.8° F), pulse 120. Is not reduced. No swelling of the parotid glands. Circumoral paleness. Marked stiffness of neck and back.

*Spinal fluid:* opalescent, 2184/3 cells, mononuclear, no bacteria. W. R. negative.

The temperature fell lytically and was normal on Nov. 26.

Nov. 28: No meningeal symptoms. Dec. 9: Discharged.

Two play-mates developed mumps 1 and 2 days after the patient had been admitted with meningitis. Further it is stated that he and the 2 boys mentioned above had played practically every day with 2 other boys, who had had mumps 2 and 3 weeks previously. Accordingly the meningitis was probably also in this case the only symptom of an epidemic parotitis infection.

***Case XII.***

(No. 2166/41). ♀ aged 6. Admitted on Dec. 9, 1941.

Previously well. Has not had parotitis.

3 days before entry she suddenly fell ill with fits of vomiting, headache; and the day before entry the patient was delirious with changing of colour, grating of teeth, grimacing, and temperature of 40° C (104° F).

*Dec. 9, on entry:* Temperature 39.8° C (103.6° F), pulse 108, completely delirious, screams loudly at the slightest touch. Inconsiderable stiffness of the neck, no swelling of the parotid glands. Kernig and Brudzinski positive. Circumoral paleness. Lucifugal.

*Spinal fluid:* absolutely clear, 490/3 cells, mononuclear. No bacteria, no growth, no pneumococci, no T. b. in culture.

The temperature fell lytically and was normal on Dec. 15 (7 days after entry).

Dec. 10: Absolutely conscious, recognizes her mother to-day.

Dec. 11: Kernig (positive).

Dec. 17: Perfectly well and natural. No stiffness of the neck. Kernig negative. Dec. 22: Discharged.

There have been many cases of epidemic parotitis in the neighbourhood. The patient's sister had mumps a fortnight previously with swelling of both parotid glands. She was rather much reduced, and there was much vomiting. The patient never had swelling of the parotid gland.

***Case XIII.***

(No. 108/42). ♀ aged 7. Admitted on Dec. 27, 1941.

Previously well. *Has not had parotitis.*

Fell ill 3 days before entry with intense headache, numerous fits of vomiting, and temperature of 40° C (104° F). There was grimacing, changing of colour, grating of teeth.

*Dec. 27, on entry:* Temperature 39.9° C (103.8° F), pulse 120. Not reduced. Circumoral paleness. Marked stiffness of the neck. Kernig and Brudzinski positive. No swelling of the parotid glands.

*Spinal fluid:* opalescent, 1500/3 cells, mononuclear. Pandy negative. No bacteria, no growth, no T. b. in culture. W. R. negative. The first 6 days treated with sulfathiazole (altogether 13 g).

The temperature fell lytically and was normal 6 days after entry (9 days after the onset of the disease).

Jan. 2: No stiffness of the neck. Kernig negative.

Jan. 17: *Spinal fluid* clear, 91/3 cells, 10 alb., 1 glob.

Jan. 18: Discharged.

*In this case the anamnesis is of vital importance to the diagnosis of mumps meningitis without swelling of the parotid gland.* Most of her class-mates had mumps. The patient went to spend her X-mas holidays with an uncle, who lived rather isolated in a district where there were no cases of mumps. 3 days after her arrival she fell ill, and as mentioned above she was admitted to the Aalborg Amtssygehus for meningitis. She does not have and has never had swelling of the parotid glands.

15 days after the onset of her disease her cousin and a child living in the house which she visited (the only children of the house) were both of them affected with mumps with considerable swelling of the parotid glands.

In this case there is no doubt that the meningitis was due to epidemic parotitis.

***Case XIV.***

(No. 102a/42). ♂ 4 years and 6 months old. Admitted on Dec. 31, 1941. Except for diphteria the patient was well previously. Has not had parotitis.

There are many cases of mumps in the neighbourhood.

Dec. 27: the patient suddenly fell ill with fever, headache, and many fits of vomiting.

Dec. 28: Temperature 40° C (104° F), but the doctor finds no cause of the fever.

Dec. 29: Temperature 39.9° C (103.8° F). Is now definitely meningeal with grating of teeth, grimacing. There is stiffness of the neck and beginning Kernig. Is treated at home with Dagenan (altogether 8 g).

*Dec. 31, on entry:* Temperature 39° C (102.2° F), pulse 124. Is reduced, pale, restless, rolls his head, changes colour, is irritable and cries a good deal.

No swelling of the parotid gland. Fauces: slight redness, otherwise nothing abnormal.

Marked stiffness of the neck. Kernig positive.

*Spinal fluid:* slightly opalescent, 1228/3 cells, mononuclear. Pandy positive, 20 alb., > 3 glob. No bacteria, no growth, no T. b. in culture. The temperature fell lytically and was normal on Jan. 5 (6 days after entry).

Jan. 5: Feeling perfectly well. No stiffness of the neck. Kernig negative. Jan. 16: Discharged.

Probably the patient got the infection from his sister, who had had mumps 2 weeks previously. The day after his admittance also his mother developed mumps.

The patient never had swelling of the parotid glands.

***Case XV.***

(No. 2268/41). ♀ aged 14. Admitted on Dec. 29, 1941.

Previously well. Has not had epidemic parotitis.

Fell ill 4 days before entry with temperature about 39° C (102.2° F), intense frontal headache and much vomiting. The day before entry she was very tired, drowsy, and occasionally delirious with slight twitches of the face. Was treated at home with Dagenan (altogether 20 tabl.). Has had no swelling of the parotid gland.

*Dec. 29, on entry:* Temperature 39.6° C (103.3° F), pulse 100, Is reduced, delirious, pale, lucifugal. Inconsiderable stiffness of the neck. Kernig and Brudzinski negative, No swelling of the parotid glands.

*Spinal fluid:* clear, 880/3 cells, mononuclear. Pandy negative. No bacteria, no growth, no T. b. in culture. W. R. negative.

The temperature fell lytically and has been normal since Jan. 3 (9 days after the onset of the disease).

Was treated with sulfathiazole the first 6 days (altogether 20 g.).

Jan. 2: Still absent and apathetic.

Jan. 5: Absolutely conscious and natural.

Jan. 13: No stiffness of the neck. Kernig negative.

Jan. 17: Spinal fluid: clear, 162/3 cells, Pandy negative.

Jan. 31: Spinal fluid: clear 39/3 cells, Pandy negative.

Febr. 7: Discharged.

Her sister developed mumps a few days before the patient was admitted for meningitis, as the only symptom of the parotitis. A few weeks previously they had both of them played with the children living next door, who by this time had mumps.

***Case XVI.***

(N. 161/42). ♂ aged 23. Admitted on Jan. 8, 1942.

*Diagnosis:* meningo-encephalitis parotitica, paresis of the left abducens nerve.

Has not previously had mumps. Many cases of mumps in the neighbourhood.

Fell ill suddenly 4 days before entry with headache, dizziness, diplopia, nausea, vomiting and temperature about 40° C (104° F). No swelling of the parotid gland.

*Jan. 8, on entry:* Temperature 38.8° C (101.8° F), pulse 84. Not reduced. No stiffness of the neck. Kernig (positive). No swelling of the parotid gland.

*Eye examination:* some hyperemia of the papillae and paresis of the left abducens nerve.

*Spinal fluid:* clear, 689/3 cells, mononuclear, 10 alb., 0 glob., no bacteria, no growth, W. R. negative, no T. b. in culture.

The temperature fell lytically and was normal on Jan. 12 (9 days after the onset of the disease).

Jan. 12: Feeling perfectly well, no headache. Jan. 16: Kernig negative.

Jan. 19: *Spinal fluid:* clear, 233/3 cells, 10 alb., 1 glob.

Jan. 26: *Spinal fluid:* clear, 112/3 cells, 10 alb., 1 glob.

Jan. 27: Discharged.

The patient had been exposed to parotitis infection 2 weeks previously.

***Case XVII.***

(No. 163/42). ♂ 2 years and 6 months old. Admitted on Jan. 12, 1942. Previously well. Has not had parotitis.

The day before entry he suddenly fell ill with numerous fits of vomiting. Was dozing, and immediately before entry he had a few convulsive attacks.

*Jan. 12, on entry:* Temperature 39° C (102.2° F), pulse 126. Is somewhat reduced. Lying with legs drawn up. Fits of twitches in arms and legs. Smacking and squint. Marked stiffness of the neck. Kernig and Brudzinski positive. No swelling of the parotid gland.

*Spinal fluid:* clear, 1990/3 cells, mononuclear, 10 alb., 1 glob, no bacteria, no growth, no T. b. in culture. W. R. negative.

Jan. 14: No meningeal symptoms, feeling perfectly well.

The temperature fell lytically and was normal 8 days after entry: (Jan. 19).

Jan. 17: *Spinal fluid:* clear, 2176/3 cells, 20 alb., 1 glob.

Jan. 27: Feeling well. Discharged.

All the children of the neighbouring family have had parotitis. 3 and 8 days before the patient was admitted with meningitis without swelling of the parotid gland, 2 brothers had developed mumps with considerable swelling of both parotid glands.

***Case XVIII.***

(No. 235/42). ♂ aged 18. Admitted on Febr. 1, 1942.

*Diagnosis:* mumps meningitis, orchitis.

Previously well. Has not had mumps.

The disease came on suddenly 2 days before entry with severe headache, some vomiting, and temperature about 39° C (102.2° F).

*Febr. 1, on entry:* Temperature 38.8° C (101.8° F), pulse 60, b. p. 95/30. Is apathetic and dozing. It is difficult to make the patient talk. Not delirious.

Marked stiffness of the neck. Kernig and Brudzinski positive. No swelling of the parotid gland.

*Spinal fluid:* opalescent, 2219/3 cells, mononuclear, 10 alb., 0 glob., no bacteria.

Febr. 3: Feeling better.

Febr. 5: *Spinal fluid:* clear, 2112/3 cells, mononuclear.

The temperature fell lytically.

Febr. 6: Normal temperature. No stiffness of the neck. Kernig negative.

Febr. 8: Temperature 39.3° C (102.7° F). To-day swelling and tenderness of the r. testis.

Febr. 12: Temperature normal, the orchitis has disappeared.

Two children living on the farm had had parotitis 3 weeks previously.

In connection with the meningitis there developed a dextral orchitis, but there was no swelling and not even tenderness of the parotid glands.

In connection with these case records I shall briefly report yet another case (similar to case XVIII), which serves as an additional verification of the theory that mumps meningitis may develop without clinical signs of parotitis.

A few years ago a patient was admitted to this department with serous meningitis of unknown etiology. There was never swelling of the parotid gland. 2 days after his admittance to hospital he developed a dextral orchitis. On a closer inquiry it appeared that he had been exposed to infection of mumps 2 weeks previously.

*The course of the disease.* Although in most of the cases the onset of the disease was rather alarming, manifesting itself with severe headache, vomiting, and high fever, occasionally also delirium and convulsions, yet all the cases were benign, in so far as all the patients recovered completely. The temperature fell lytically in the course of 5 to 10 days; the average duration of the fever was 1 week. The meningeal symptoms vanished within the same space of time[1]. In a great number of our patients there were prostration and deliries, and in several cases there was no relation between the degree of the disease and the number of cells in the spinal fluid. In one case (case record XVI) there was also found paresis of the abducens nerve.

In the spinal fluid, which was clear or slightly opalescent, there was found a marked increase in cells, chiefly mononuclear. But the amount of albumin and globulin was found to be normal or only slightly increased.

Generally the meningeal symptoms vanished in the course of 1 week, whereas the increase in cells would often subsist for rather a long time, and the patients were discharged in spite of the increased number of cells in the spinal fluid.

The maximum number of cells in the material was 3104/3. The cell figures appear from the following:

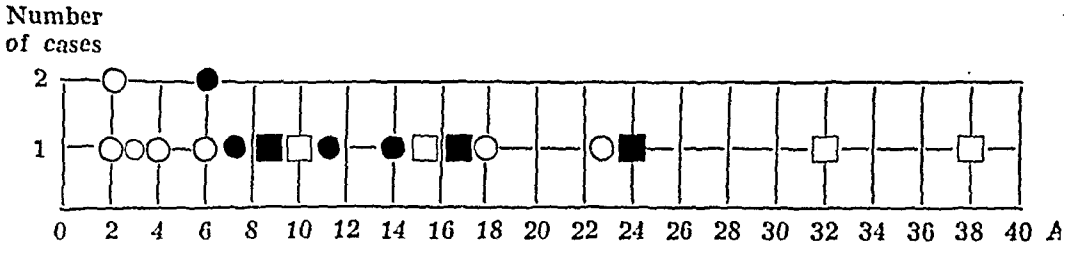
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[1] Chemotherapy was without any effect.

| *Number of cells.* | *Number of cases.* |
|---|---|
| 3200/3—1000/3 | 12 |
| 1000/3—500/3 | 3 |
| 500/3—100/3 | 3 |

In my material mumps meningitis was only found in rather young individuals (maximum age 38).

Age and distribution of sex appears from the following diagram.




○ = ♂ pt. with mumps meningitis without parotitis.
● = ♀ » » » » » »
□ = ♂ » » » » with parotitis.
■ = ♀ » » » » » »

*The diagnosis* is often difficult to make at the onset of the disease. At first we believed the disease to be *aparalytic poliomyelitis*, but the continued admittance of new patients with serous meningitis without the slightest signs of paresis made us relinquish this diagnosis. Moreover, at the onset of poliomyelitis there are often found leukocytes in the spinal fluid, whereas no leukocytes were found in our cases.

The differential diagnosis against *tubercular meningitis* can only be made with certainty through the course of the disease. All cases having been benign, the tubercular meningitis can be left out of account. Practically all spinal fluids were examined bacteriologically, and in no case did we find T. b. in culture.

In the period (November to February) in which we received the patients with serous meningitis there was a severe parotitis epidemic, and moreover we received 7 patients with parotitis accompanied by meningitis, therefore it was natural to suppose that the above mentioned cases of *serous meningitis were due to a special manifestation of the parotitis infection.* And the supposition was confirmed by the fact that in all these cases there proved to be epidemic

parotitis in the immediate surroundings of the patients, and besides, the course of the disease corresponded exactly to that of the cases of meningitis developed in patients with obvious epidemic parotitis. The meningitis appeared exclusively in rather young individuals (8 out of the 11 patients were children under 11 years of age), and chiefly in male patients.

None of the patients had previously had parotitis, but even if this had not been the case, it does not exclude the diagnosis of *mumps meningitis*, as during this epidemic we saw numerous cases of severe parotitis in patients who had previously had mumps.

Some of the cases of serous meningitis which within recent years have been described under the diagnosis of *»meningitis acuta serosa idiopatica benigna»* were probably in reality cases of *mumps meningitis without swelling of the parotid gland.*

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*Mumps meningitis with special reference to cases without swelling of the parotid gland.*

The auther reports eighteen cases of mumps meningitis. In six of the cases the meningitis was followed by swelling of the parotid gland, and in one case only tenderness, while the meningitis in eleven cases was the only manifestation of the mumps-infection. The diagnosis was verified by the characteristic and uniform course and especially by the epidemiological circumstances.

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(Aus der Rheuma-Abteilung des Akademischen Krankenhauses in Lund, Schweden. Direktor: Prof. Dr. Sven Ingvar.)

# Klinische Studien über den chronischen Gelenkrheumatismus.

## III. Die prodromalen Krankheitsbilder.

Von

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(Bei der Redaktion am 12. Januar 1942 eingegangen).

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### Febris rheumatica c. Arthritis chron.

Es ist eine alte klinische Erfahrung, dass dem akuten Polyarthritissyndrom oft eine akute Tonsillitis oder andere infektiöse Zustände des Rachens, der Mundhöhle oder der oberen Luftwege vorangehen. Je nachdem, wie die Anschauungen über die Ätiologie und Pathogenese der Febris rheumatica gewechelt haben, waren auch die Ansichten über Natur und Bedeutung dieser prodromalen infektiösen Zustände verschieden.

Um die Jahrhundertwende galt das rheumatische Fieber gemeinhin als eine spezifische Infektionskrankheit, und diese prodromalen Krankheitszustände betrachtete man als nicht zu dem eigentlichen Krankheitsbild gehörig, sondern man mass ihnen nur die Rolle prädisponierender Momente bei.

Der heutige Standpunkt in dieser Frage ist ja keineswegs einheitlich. Gewisse Forscher, so die deutschen Pathologen Aschoff, Fahr und Gräff, sind fortwährend der Ansicht, es handle sich um eine spezifische Infektionskrankheit (*Rheumatismus infectiosus specificus*). Doch stehen sie auf dem Standpunkt, dass hier ebenso wie bei Scarlatina, Morbilli usw. der prodromale infektiöse Zustand

als ein Bestandteil des spezifischen Krankheitsverlaufes selbst anzusehen sei. Dieser Ansicht sind auch diejenigen Forscher, die mit Bach, Dawson, Coburn, Poynton, Schlesinger, Swift, Veil u. a. das rheumatische Fieber auf eine Infektion durch hämolytische Streptokokken zurückführen. Die Forscher dagegen, die wie Klinge, Müller, Rössle, Talalajew u. a. das rheumatische Fieber nicht als eine Infektionskrankheit im eigentlichen Sinne sehen wollen, sondern statt dessen mehr als eine spezielle hyperergische Gewebsreaktion, ein Parallelbild der Serumkrankheit und anderer anaphylaktischer Zustände, betrachten diese prodromalen Infektionen als selbständig. In der sich an diese anschliessenden stillen Periode geschieht dann nach diesen Autoren das Wesentliche, nämlich dass der Organismus hyperergisch wird und sich so darauf einstellt, in der speziellen hyperergischen Art und Weise zu reagieren, wodurch es zu diesen klinischen rheumatischen Krankheitsbildern kommt.

Ist man schliesslich der Ansicht, dass das rheumatische Fieber zwar primär durch eine Infektion mit hämolytischen Streptokokken verursacht wird, dass aber das Zustandekommen dieser klinischen Syndrome und Krankheitsbilder eine hyperergische Reaktion des betreffenden Organismus gegenüber dieser Infektion zur Voraussetzung hat — die Ansicht, die dem Verf. auf der Grundlage der gegenwärtig vorliegenden klinischen, bakteriellen und serologischen Tatsachen als die annehmbarste erscheint — so müssen diese Prodrome als die Primärinfektion betrachtet werden.

Mag nun die eine oder andere dieser Ansichten richtig sein, oder vielleicht auch keine, jedenfalls ist es von Interesse festzustellen, in welchen Erscheinungsformen und mit welcher Häufigkeit verschiedene infektiöse Zustände als Prodrome vor dem eigentlichen klinischen Ausbruch des rheumatischen Fiebers auftreten.

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Von diesen prodrodromalen Infektionen bei der Febris rheumatica ist nun die akute Tonsillitis die am häufigsten begegnende. Schon Heberden schrieb von der Tonsillitis: »Finito morbo, nonnulli adoriuntur dolores et tumores rheumatici.» Und bereits Brown lenkte auch die Aufmerksamkeit darauf, dass zufolge seinen Untersuchungen die Frequenz des rheumatischen Fiebers und der akuten Tonsillitis sowohl zeitlich als räumlich oft parallel zu- oder ab-

nahm, eine Parallelität, auf die von modernen Autoren u. a. Coburn, Edström, Glover und Schlesinger hingewiesen haben. Es ist jedoch zu beachten — wie Glover auch besonders hervorgehoben hat — dass dabei die Höhepunkte der Tonsillitisepidemien stets etwa 2 Wochen bis 1 Monat vor dem entsprechenden Höhepunkt im Auftreten der Febris rheumatica zu verzeichnen sind.

Dass *die akute Tonsillitis* die am häufigsten zu beobachtende prodromale Infektion vor dem Auftreten des rheumatischen Fiebers ist, zeigte auch eine von Edström in den Jahren 1934—35 ausgeführte Untersuchung von 850 an der Lunder Medizinischen Klinik unter der Diagnose des akuten Gelenkrheumatismus behandelten Fällen. Die betreffenden Fälle waren insgesamt 1.227mal an einem einwandfrei gesicherten klinischen Polyarthritissyndrom erkrankt, und die Anamnese verzeichnete in 524 Fällen, d. i. 41 %, kurz vor diesem klinischen Krankheitsbeginn eine sicher festgestellte akute Tonsillitis, eine Zahl, die in bester Übereinstimmung steht mit der von Motzfeldt zur gleichen Zeit in einer entsprechenden Untersuchung ermittelten Zahl von 40 %.

**Tabelle 1.**

Bei 850 in der med. Klinik des akad. Krankenhauses in Lund unter der Diagnose »Polyarthritis rheumat. acut.« gepflegten Patienten, die insgesamt 1.227 Male sicher unter diesem klinischen Krankheitsbild erkrankten, waren in der Zeit kurz vor dieser Erkrankung folgende infektiösen Zustände vorhanden.

| Infektiöser Zustand | Anzahl Fälle | % von Sämtlichen |
|---|---|---|
| Tonsillitis acut., Peritonsillitis | 524 | 41 |
| Pharyngitis; Laryngitis, »Erkältung«, Otitis, Sinuitis, etc. | 284 | 24 |
| Apicale Zahngranulomen, Paradentitis | 15 | 1 |
| Thrombophlebitis | 5 | |
| Appendicitis acut. | 6 | |
| Gastritis, Enterocolitis | 7 | |
| Cholezystitis | 4 | |
| Pyelozystitis, Zystitis | 5 | |
| Salpingitis acut. | 2 | |
| Dacryozystitis acut. | 1 | |
| Carbunculus, Furunculus, Abszessus, usw. | 6 | |
| Anzahl der Fälle ohne solche prodromalen Infektionen | 356 | 29 |

Bei der Untersuchung der 242 Fälle von Febris rheumatica c. Arthritis chron., die in den Jahren 1929—33 an der hiesigen Rheuma-Klinik behandelt und in den früheren Arbeiten dieser Serie eingehender beschrieben worden sind, wurde ebenfalls festgestellt, dass die akute Tonsillitis der häufigste prodromale Infektionszustand ist. Bei den 602 sicher festgestellten Erkrankungen an einem akuten Polyarthritissyndrom, welche bei der Nachuntersuchung für diese 242 Fälle verzeichnet wurden — als akut wird dieses Syndrom hier ebenso wie in der vorigen Untersuchung mit Hinsicht auf den akuten Krankheitsbeginn betrachtet, doch ohne Rücksicht darauf, ob es evtl. im späteren Verlauf mehr oder weniger chronisch wurde — zeigte es sich, dass 297mal, also in 49 %, in der Zeit kurz vor diesem klinischen Krankheitsbeginn eine akute Tonsillitis oder Peritonsillitis vorgelegen hatte, also in einem noch höheren Prozentsatz als in der vorgenannten Untersuchung. Die Ursache dessen dürfte darin zu erblicken sein, dass diese klinische Gruppe, wo das akute Polyarthritissyndrom, das den Patienten in die Klinik führte, ausnahmslos mehr oder weniger in das chronische Stadium überging, in grösserem Ausmass als die erstere Gruppe Recidive aufwies — vgl. die früher von Edström getroffene Feststellung, dass die Tendenz eines mehr chronischen Charakters des Polyarthritissyndroms bei den Febris-rheumatica-Fällen um so stärker wird, je mehr Recidive auftreten (während 346 Fälle nicht recidivierenden Typs ein chronisches Polyarthritissyndrom in 30 Fällen, d. i. 9 %, aufwiesen, wurde in 86 Fällen von Febris rheumatica derselben Serie mit 3 oder mehr Recidiven ein solches chronizitierendes Syndrom in 47 Fällen, d. i. 55 %, verzeichnet; siehe »Febris rheumatica» S. 114) — sowie dass *bei recidivierenden Fällen prodromale akute Tonsillitis häufiger ist als bei nicht recidivierenden.*

Als das nächst der akuten Tonsillitis am häufigsten begegnende Prodrom erweisen sich die *Infektionen des Nasopharynx und seiner Umgebung,* Laryngitis, Pharyngitis, Rhinitis, *Otitis, Sinuitis* usw. In der ersten klinischen Gruppe trat ein solches Syndrom in 284 Fällen (24 %) auf, in der zweiten Gruppe in einer etwas kleineren Zahl, nämlich 114 Fällen (19 %).

In nicht weniger als 808 Fällen oder 65 % der ersten Gruppe von Febris-rheumatica-Patienten und in 411 Fällen oder 68 % der letzteren sind also prodromale Infektionen der Tonsillen, des Nasopharynx oder seiner Umgebung festgestellt worden. Dies

**Tabelle 2.**

Bei 242 in der Rheuma-Klinik des akad. Krankenhauses in Lund unter der Diagnose »Febris rheumatica c. arthritis chron.» gepflegten Patienten, die insgesamt 602 Male sicher unter einem von den klinischen Krankheitsbildern des rheumatischen Fiebers erkrankt waren, waren in der Zeit kurz vor dieser Erkrankung folgende infektiösen Zustände vorhanden.

| Infektiöser Zustand | Anzahl Fälle | % von Sämtlichen |
|---|---|---|
| Tonsillitis acut., Peritonsillitis | 297 | 49 |
| Pharyngitis, Laryngitis, »Erkältung», Otitis, Sinuitis, usw. | 114 | 19 |
| Apikale Zahngranulome, Paradentitis | 7 | 1 |
| Thrombophlebitis | 1 | |
| Carbunculus, Phlegmone | 3 | |
| Erysipelas | 1 | |
| Appendicitis acut. | 1 | |
| Pyelozystitis, Zystitis | 2 | |
| Urethritis | 1 | |
| Salpingitis acut. | 2 | |
| Cholezystitis | 1 | |
| Anzahl der Fälle ohne solche prodromalen Infektionen | 172 | 28 ½ |

spricht unleugbar dafür, dass die Infektion bei der Febris rheumatica — mag nun diese prodromale Infektion für das Auftreten der Krankheit von direkter oder indirekter Bedeutung sein — diesen Weg nähme. Branson spricht auch von den oberen Atmungswegen als »the avenue of rheumatic infection».

In diesem Zusammenhang verdient bemerkt zu werden, dass wir an der hiesigen Rheuma-Klinik dieselbe Feststellung wie Coburn, McCulloc u. Irvine-Jones, Schlesinger, Sheldon, Swift, Weinstein u. Styron und andere gemacht haben, nämlich dass im Zusammenhang mit diesen prodromalen Tonsillitiden, Pharyngitiden, Otitiden, Sinuitiden u. a. Infektionen der oberen Rachen- und Luftwege in grossem Ausmass Streptokokken — im allgemeinen Streptococcus haemolyticus — in diesen Wegen nachzuweisen sind und zwar in einem weit höheren Prozentsatz als bei Gesunden, was unstreitig bis zu einem gewissen Grade für die Bedeutung dieser Bakterien in diesen Zusammenhängen spricht.

*Zahninfektionen*, meist marginale Paradentitiden und apikale Granulome, treten ebenfalls in einer gewissen Zahl von Fällen pro-

dromal auf. Bei der ersteren Klientel fanden sich solche in 15 Fällen (1 %), bei der letzteren in 7 Fällen (ebenfalls 1 %) — die betreffenden Patienten hatten also während der dem Krankheitsbeginn vorangegangenen Wochen Zahnschmerzen, Zahngeschwüre o. dgl. gehabt. Ausserdem erhob jedoch die klinische Untersuchung nach der Krankenhausaufnahme noch bei weiteren 27 Fällen der letztgenannten Klientel röntgenologisch den Befund apikaler Granulome, die bis dahin keine klinischen Symptome gegeben hatten und die bei der Extraktion sämtlich verifiziert wurden. Es ist indessen sehr schwierig, diese Befunde zu beurteilen. Es ist ja nicht ausgeschlossen, dass es sich um reine Parallelbefunde handeln kann — weder das rheumatische Fieber noch die apikalen Granulome gehören ja zu den Seltenheiten. Dass diesen Zahninfektionen wirklich dieselbe grundsätzliche Bedeutung als Prodrom zu zusprechen wäre, wie z. B. der Tonsillitis, ist noch nicht als bewiesen anzusehen. Doch verdient in diesem Zusammenhang erwähnt zu werden, dass wir an der hiesigen Klinik in nicht ganz wenigen Fällen die Feststellung haben machen können, dass der rheumatische Prozess, teils die klinische Arthritissymptome, teils die klinischen Endocarditissymptome, teils Veränderungen der S.R., im Zusammenhang mit der Zahnsanierung in diesen Granulomfällen ein vorübergehendes Aufflammen und anschliessend endgültige Besserung gezeigt haben. Es handelt sich hier jedoch nicht um eindeutige Befunde, und ich werde noch darauf zurückkommen.

*Sonstige prodromale infektiöse Zustände* sind in beiden Untersuchungsreihen selten, und wenn man auch nicht die Möglichkeit ausschliessen kann, dass hier echte Prodrome vorgelegen haben, darf man auch andererseits nicht die Möglichkeit eines rein zufälligen Zusammentreffens zweier voneinander gänzlich unabhängiger krankhafter Zustände bei einem und demselben Patienten ausschliessen.

Meyer und Schmidt haben die *Thrombophlebitis* als Prodromalsyndrom bei akutem Gelenkrheumatismus ausführlich erörtert und ich verweise diesbezüglich auf ihre Arbeiten.

Die *banale Urethritis* als Prodromalsyndrom tritt besonders bei dem sog. Reiter'schen Syndrom auf, worauf in einem anderen Zusammenhang zurückzukommen sein wird.

Schliesslich hat sich in einem knappen Drittel der Fälle (29 % bzw. 28 ½ %) kein prodromaler Infektionszustand feststellen lassen.

Sieht man dies vor dem Hintergrunde, dass es in einer anderen Untersuchungsreihe von durchaus ebenbürtigem Material von Febris-rheumatica-Fällen aus derselben Klinik gelungen ist, in über 90 % der Fälle einen positiven Antistreptolysin- und Antifibrolysintiter nachzuweisen (Winblad), sowie dass bei einer sehr grossen Zahl solcher klinischen Krankheitsfälle ohne prodromale Erscheinungen diese Titer doch positiv waren, so hat man einen weiteren wichtigen Punkt zu berücksichtigen, wenn die Bedeutung des hämolytischen Streptococcus für die Genese dieser traumatischen Krankheitszustände zur Diskussion steht.

## Polyarthritis rheumat. chron.

In der zweiten Gruppe des letzteren Materials, den an der hiesigen Rheuma-Klinik zur Behandlung gelangten 262 Fällen von Polyarthritis rheumat. chron., die ebenfalls in den früheren Arbeiten dieser Serie eingehender beschrieben worden sind, waren prodromale infektiöse Zustände vor dem Auftreten des Polyarthritissyndroms in weit geringerem Ausmass zu verzeichnen. Nun ist freilich zu bedenken, dass es sehr oft äusserst schwierig ist festzustellen, wann ungefähr das schleichende Polyarthritissyndrom eigentlich begonnen hat — wie aus der vorigen Arbeit dieser Reihe hervorging, konnte bloss in 153 Fällen der 262 auch nur der Monat des Krankheitsbeginns ermittelt werden — die ersten Symptome, beispielsweise in Form einer leichten Schmerzhaftigkeit bei Bewegungen der proximalen Fingergelenke, kalter Hände und Füsse, allgemeiner Mattigkeit und Müdigkeit usw., sind ja so unbestimmten Charakters, dass es sehr schwierig sein kann, nachträglich ihr Auftreten zeitlich genau zu bestimmen. Deshalb gestaltet sich auch die nachträgliche Beurteilung dessen recht schwierig, inwiefern im Einzelfall eine Erkältung, eine Tonsillitis oder eine andere Infektion in den Wochen kurz vor dem ungefähren Krankheitsbeginn als ein Prodrom zu werten ist oder nicht. Sind die leichtesten unbestimmten Beschwerden z. B. an den Fingergelenken bereits vor der fraglichen Infektion aufgetreten, so kann diese natürlich nicht prodromalen Charakters gewesen sein — sie kann in solchen Fällen jedoch insofern von Einfluss sein, als sie die Widerstandskraft des angegriffenen Organismus in der ersten kritischen Zeit schwächt, ein Faktor, den man ganz natürlich nicht ausser acht lassen darf.

Andererseits sind Erkältungen, Tonsillitiden und andere Infektionen der oberen Rachen- und Luftwege wenigstens in der kälteren Jahreszeit auf unseren Breitengraden so häufig, auch bei »Gesunden», dass dem Spiel des Zufalls eine grosse Rolle beizumessen sein dürfte.

Nimmt man, von dieser Erwägung ausgehend, Tabelle 3 in Augenschein, so drängen sich starke Bedenken auf.

**Tabelle 3.**

Bei 262 in der Rheuma-Klinik des akad. Krankenhauses in Lund unter der Diagnose »Polyarthritis rheumat. chron. (infect.)» gepflegten Patienten waren in der Zeit kurz vor dieser Erkrankung folgende infektiösen Zustände vorhanden.

| Infektiöser Zustand | Anzahl Fälle | % von Sämtlichen |
|---|---|---|
| Tonsillit. acut., Peritonsillitis | 26 | 10 |
| Pharyngitis, Laryngitis, »Erkältung», Otitis, Sinuitis, usw. | 17 | 5 |
| Zahnweh, Zahnabszess | 6 | |
| Diphterie | 1 | |
| Carbunculus, Phlegmone | 3 | |
| *Appendizitis acut.* | 2 | |
| Enteritis acut | 1 | |
| Cholezystitis | 4 | |
| Pyelozystitis, Zystitis | 2 | |
| Urethritis | 2 | |
| *Salpingitis, Cervicitis, usw.* | 6 | |
| Anzahl der Fälle ohne solche prodromalen Infektionen | 192 | 73 |

Wie man sieht, findet sich hier nur in 26 Fällen, d. i. 10 %, eine prodromale Tonsillitis oder Peritonsillitis, in weiteren 18 Fällen haben andere Infektionen der oberen Luftwege bestanden, sowie in 6 Fällen Zahngeschwüre oder Zahnschmerz. *Insgesamt sind also in nur 50 Fällen, d. h. 19 %, prodromale Infektionen der Mundhöhle, des Rachens oder der oberen Luftwege zu verzeichnen.* In nicht weniger als 192 Fällen oder 73 % des Gesamtmaterials war keine prodromale Infektion festzustellen. Wie viele Prozent der ersten Gruppe sind auf das Spiel des Zufalls zurückzuführen? *Gibt es überhaupt hier einen ursächlichen Zusammenhang von derselben oder analoger Bedeutung wie bei den Febris-rheumatica-Fällen?*

Es ist jedoch zunächst darauf hinzuweisen, dass man hier in vielleicht noch grösserem Ausmass als bei den Febris-rheumatica-Fällen bei der klinischen Untersuchung im Krankenhaus örtliche Infekte feststellt, wie apikale Zahngranulome, marginale Paradentitiden, Sinuitiden, Pharyngitiden, ja, sogar Cholecystitiden, Cystitiden, Cervicitiden usw., die entweder keine oder nur so geringe klinische Symptome gesetzt hatten, dass der Patient sie vor der Klinikaufnahme ganz unbeachtet gelassen hatte, weshalb sie hier nicht als Prodrome gewertet worden sind. Als ein Beispiel sei erwähnt, dass von den augenblicklich, Nov. 1941, in der Klinik befindlichen 43 Patienten mit typischer chronischer rheumatischer Polyarthritis nicht weniger als 7 apikale Zahngranulome hatten, die nicht nur röntgenologisch, sondern auch klinisch operativ verifiziert worden sind, von denen aber nur eines vor dem kürzlich in der Klinik erhobenen röntgenologischen Befund klinische Symptome gegeben hatte. Bei einer früheren Zusammenstellung von 106 solchen chronischen Polyarthritiden, die sehr sorgfältig auf etwaige örtliche entzündliche Herde untersucht worden waren, zeigte es sich auch, dass solche in nicht weniger als 87 der 106 Fälle nachgewiesen werden konnten (Den Norske Tannlægeforenings Tidende 1935, H. X). Die hier untersuchten 262 Fälle sind in dieser Beziehung während des Klinikaufenthaltes nicht so eingehend geprüft worden, doch konnten auch hier in 42 Fällen nach der Klinikaufnahme röntgenologisch apikale Zahngranulome nachgewiesen werden, die keine klinischen Symptome ergeben hatten und die sich bei der Extraktion verifizierten.

Von dem sehr schwierigen Problem der Bedeutung der prodromalen Infektion für die Entstehung des rheumatischen Krankheitszustandes kommen wir zu dem noch schwereren Problem der entsprechenden Bedeutung der sog. »Fokalinfektion.» Auf den ersten Blick scheint es sich in beiden Fällen um ein und dasselbe Problem zu handeln, doch besteht ein gewisser Unterschied. So z. B. erscheint es einem einleuchtender, dass eine akute Zahninfektion, die sich klinisch u. a. durch Zahnschmerz bemerkbar gemacht hat, als Prodromalsyndrom in der bereits hinsichtlich des rheumatischen Fiebers berührten Art und Weise ihre Bedeutung gehabt haben kann, als dass eine chronische, verhältnismässig wohlbegrenzte und leichte Infektion, meist mit relativ niedrigvirulenten Bakterienstämmen, wie es bei dem apikalen Zahngranulom meist

der Fall ist, eine analoge Bedeutung haben könnte. Ebenso besteht ein gewisser Unterschied zwischen der Bedeutung der akuten, meist recidivierenden Tonsillitis als Prodromalsyndrom und der Bedeutung der sog. chronischen Tonsillitis als Fokalinfektion, namentlich da dieser letztere Zustand ja sowohl pathogenetisch als klinisch und therapeutisch so umstritten ist.

Ist man hinsichtlich der Bedeutung der prodromalen Infektion für die Entstehung des rheumatischen Krankheitszustandes bei diesen chronischen Arthritiden im Zweifel, so ist dies in noch höherem Grade der Fall, wenn man zur Frage nach der entsprechenden Bedeutung der Fokalinfektion kommt. Der Verf. neigte früher zu der Ansicht (Den Norske Tannlægefor. Tidskr. H. X, 1935), dass es zwar schwer, wenn nicht unmöglich sei, die Fokalinfektionslehre in ihrer ursprünglichen Gestalt, wie sie von Rosenow, Billings und, anderen, hauptsächlich amerikanischen Autoren inauguriert wurde mit unserer klinischen Erfahrung in Einklang zu bringen, dass aber doch eine gewisse bessere Übereinstimmung mit der klinischen Erfahrung vorliegen kann, wenn man das Problem unter dem Gesichtswinkel betrachtet, dass diese sog. Fokalinfektionsherde Herde sind, die Immunitätsreaktionen hervorrufen.

Seitdem sind indessen allerlei Erkenntnisse hinzugekommen, die das Problem noch ungewisser gestalten. So fand z. B. Brown unter einem grossen Material aus einer psychiatrischen Klinik Foci in demselben Prozentsatz bei denjenigen Fällen dieses Materials, die Arthritiden hatten, wie bei der übrigen Klientel, und Steindler stellte unter 3004 Fällen von »atrophic arthritis» Herde in dem gleichen Prozentsatz (17 %) fest wie unter 1335 Fällen von »hypertrophic arthritis», welch letztere Gruppe zwar eine Reihe von Fällen mit sekundären reaktiven Gelenkveränderungen im Zusammenhang mit einem arthritischen Prozess enthält, hauptsächlich aber doch Gelenkprozesse rein degenerativen Typs. In einer kritischen Übersicht haben kürzlich auch Reimann u. Havens über die einschlägige Literatur der letzten Jahre berichtet. Sie kommen zu dem Schluss, dass die Fokalinfektionslehre der Kritik nicht hat standhalten können, sondern auf sehr unsicherer Grundlage ruht. Je mehr man sich in das sehr reiche einschlägige Schrifttum vertieft, um so mehr ist man geneigt, diese Auffassung nicht zu vernachlässigen.

Von den Fürsprechern der Fokalinfektionslehre ist dagegen ein-

gewandt worden, am entscheidendsten für die Frage, ob diese Herde für das nachfolgende klinische Krankheitsbild von Bedeutung sein können, sei es jedenfalls, ob dieses im direkten Anschluss an die Sanierung eines solchen Herdes auffallend und endgültig beeinflusst wird. Solche Fälle sind in grosser Zahl veröffentlicht worden, und auch unter unserer Klientel finden sich Fälle, wo gerade in direktem Anschluss an die Tonsillektomie, die Aufmeisselung der Sinuitis oder die Extraktion des infizierten Zahnes die S. R.-Werte stiegen, die Arthritiserscheinungen in dem einen oder andern Gelenk aufflammten, eine heftige Peritendinitis, ein paar subcutane Noduli usw. auftraten, worauf der Prozess in den nachfolgenden Wochen klinisch eine auffallende Wendung zum Besseren zeigte, so dass das Endergebnis eine wesentliche Besserung oder Ausheilung des klinischen rheumatischen Syndroms war.

Es lässt sich darüber diskutieren, wie nun die Einwirkung der Herdinfektion auf den rheumatischen Krankheitsprozess sich etwa abspielen kann. Nach der Fokalinfektionslehre kann eine direkte Einwirkung der mesenchymalen Gewebe durch Metastasierung von Krankheitsvirus in Frage kommen, also eine Sepsis, oder auch eine indirekte Einwirkung auf immunbiologischem Wege durch das Zustandebringen der hyperergischen Reaktionsweise und damit das Hervorrufen der klinischen Krankheitsbilder der mesenchymalen Organe. Bei diesen chronischen rheumatischen Polyarthritiden sind theoretisch beide Arten von Einwirkung möglich; wir begegnen hier der ganzen Skala von septischen Arthritiden bis zu hyperergischen Arthritiden entsprechend wie bei der Febris rheumatica (siehe Acta Med. Scand. 103. 90. 1940). Slauck drückt sachlich dasselbe auf etwas andere Weise aus, indem er diese chronischen Arthritiden in fokalinfektiöse und fokaltoxische aufteilt, wobei er für die letztere Gruppe annimmt, dass die indirekte Einwirkung seitens der Foci auf die mesenchymalen Organe auf neuralem Wege erfolt.

Aber man darf dabei doch nicht die dritte Möglichkeit vergessen, dass nämlich kein direkter Zusammenhang zwischen dem örtlichen entzündlichen Herde, der sog. Fokalinfektion, und der allgemeinen rheumatischen Infektion besteht, sondern dass der Grund dafür, dass eine Korrelation zwischen ihnen in solchen Fällen anscheinend zu erkennen ist, darin liegt, dass beide Infektionen, obwohl ohne Zusammenhang untereinander, doch auf denselben

Organismus einwirken, dessen Widerstandskraft auf diese Weise wie in einem Kampfe angegriffen wird, wo auf der einen Seite ein, auf der andern Seite zwei Gegner stehen, die alle gegenseitig verfeindet sind.

Auch hier, bei den chronischen rheumatischen Polyarthritiden, begegnet man der interessanten Tatsache, dass die Antistreptolysin- und Antifibrolysintiter in einem höheren Prozentsatz (etwa 35 %) positiv sind (Winblad) als der Prozentsatz, in welchem klinische prodromale Infektionsbilder nachgewiesen werden konnten. Die Bedeutung dieses Befundes verringert sich jedoch durch die obenerwähnte vielfache Feststellung von Herdinfekten u. a. mit hämolytischen Streptokokken auch in Fällen, wo klinische Symptome solcher Herde nicht vorgelegen hatten.

## Zusammenfassung.

242 Fälle von Febris rheumatica c. arthritis chron. und 262 Fälle von Polyarthritis rheumat. chron. sind hinsichtlich ihrer prodromalen Krankheitsbilder untersucht worden.

In diesem ersteren Material waren in der Zeit unmittelbar vor dem klinischen Ausbruch des akuten Polyarthritis-Syndroms klinische Zeichen einer Tonsillitis oder Peritonsillitis bei 49 % der Fälle (297mal von 602 sicher festgestellten Erkrankungen) und Zeichen eines anderen infektiösen Zustands in Naso-Pharynx, Larynx und Ohrengegend in 19 % (114mal von 602 Erkrankungen) vorhanden. In 28 ½ % war kein prodromaler infektiöser Zustand mit bestimmtheit zu konstatieren.

In der letzteren Hälfte des Materials, die Fälle von Polyarthritis rheumat. chron., waren die entsprechenden Hundertsätze 10 %, 5 % und 73 %. Insgesamt in nur 50 Fällen, d. h. 19 %, waren hier prodromale Infektionen der Mundhöhle, des Rachens oder der oberen Luftwege zu verzeichnen. Wie vieles ist hier auf das Spiel des Zufalls zurückzuführen? Gibt es überhaupt hier einen Zusammenhang von derselben oder analogen Bedeutung wie bei den Febris-rheumatica-Fällen?

Die Frage der Bedeutung der Fokalinfektion wird im Anschluss daran kurz gestreift.

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(Aus der Rheuma-Abteilung des Akademischen Krankenhauses in Lund, Schweden. Direktor: Prof. Dr. Sven Ingvar.)

# Klinische Studien über den chronischen Gelenkrheumatismus.

## IV. Trauma und Rheumatismus.

Von

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Untersuchungen mehrerer Forscher, besonders solche von Fahr, Klinge und Talalajew, haben gezeigt, dass die beiden Komponenten des rheumatischen Gewebsbildes — die exsudativ-degenerative und die proliferative — in gewissen Fällen fast parallel verlaufen können, während in anderen Fällen mal die eine, mal die andere dieser beiden Komponenten vorherrscht, was für das pathologisch-anatomische Bild von grosser Bedeutung ist. Wie sich das Bild im Einzelfall gestaltet, hängt in erster Linie von der eigenen Virulenz und Natur des rheumatischen Prozesses ab, ausserdem jedoch auch von dem Alter und der Konstitution des Kranken sowie von der Lokalisation des Prozesses. Nach den Untersuchungen Frank's und Talalajew's dominiert nämlich die proliferative Komponente, wenn der Prozess seinen Sitz im Myokard hat, während hingegen bei den rheumatischen subkutanen Noduli die exsudativ-degenerative Komponente vorherrscht.

Das histologische Bild wird dabei von funktionell-mechanischen Momenten bestimmt. *Je stärker das Gewebe aktiv oder mechanisch beansprucht wird, um so deutlicher und umfassender tritt die Zellwucherung der rheumatischen Knötchen, die proliferative Komponente, in Erscheinung.* Die rheumatischen Gewebsschäden in

Myokard, Zwerchfell, Schlundmuskel und Mandelumgebung, gelenknahem Sehnengewebe, herznahen Arterienwänden, herzfernen Arterienwänden, peripheren Nerven und Subcutis zeigen in der hier genannten Reihenfolge eine mehr und mehr dominierende exsudativ-degenerative Komponente.

Wenn also die Gestaltung der rheumatischen Gewebsschädigung gesetzmässig durch den Grad der funktionell-mechanischen Belastung bestimmt wird, der das einzelne Gewebe oder Organ ausgesetzt ist, so lässt sich dasselbe auch bezüglich der Lokalisation der rheumatischen Gewebsschäden innerhalb des kranken Organs feststellen.

Als ein Beispiel dessen kann *die rheumatische Gewebsschädigung in Myo- und Endokard* dienen. Die stärksten Gewebsveränderungen und Prozesse sehen wir hier in den basalen Teilen der Klappen — eine Valvulitis — namentlich in der arteriellen Herzhälfte, den Teilen des Herzens, die funktionell-mechanisch am meisten beansprucht sind.



Bild 1.
Subkutane rheumatische Noduli am Hinterschädel bei einem Kinde.



2 A



2 B



2 C

Bild 2.

*Subkutane rheumatische Noduli* A) in der Ellenbogengegend über der Ulnarkante; B) an den Fingerknöcheln; C) an einem Daumen.

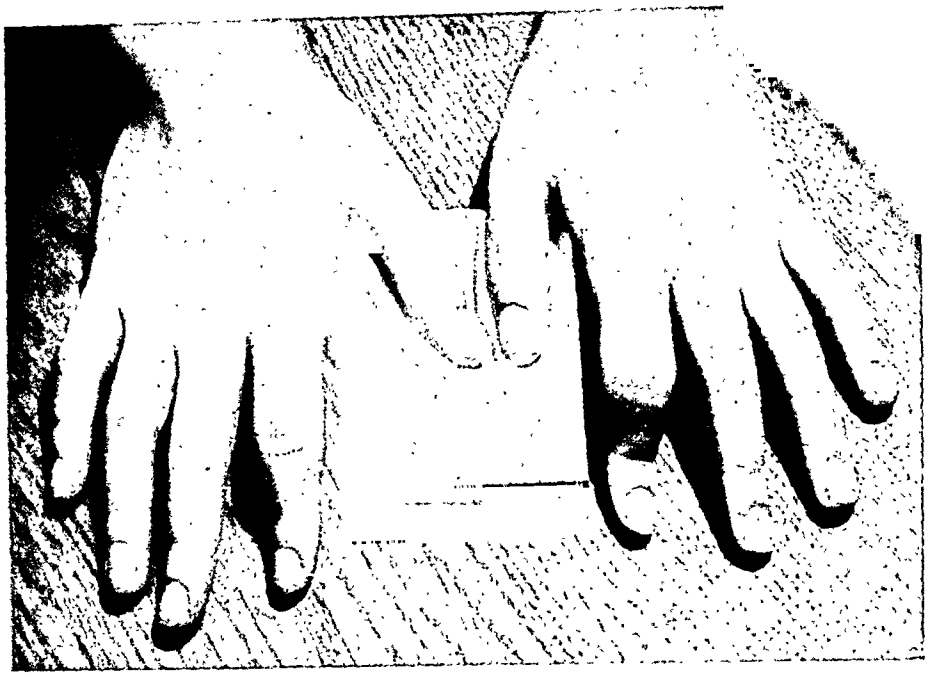


Bild 3.

Ein Fall von Polyarthritis rheumat. chron. mit den proximalen Fingergelenken I und II der rechten Hand und II der linken Hand angegriffen. Am Anfang des Prozesses.

Dasselbe gilt von der *Lokalisation der subkutanen rheumatischen Noduli.* Mit Vorliebe findet man sie an Stellen des Körpers, die mehr als andere äusserer Gewalteinwirkung durch Stösse u. dgl. ausgesetzt sind, in der Ellbogengegend über der Ulnarkante, der Knie- und der Fersengegend, an den Fingerknöcheln und -spitzen usw. Zu beachten ist schliesslich, dass man sie beim Kinde — der Säugling hat keine rheumatischen Prozesse — auch am Hinterschädel sieht, eine beim Erwachsenen äusserst seltene Lokalisation, welch letzterer ja auch im Gegensatz zum Kinde höchst selten diese Stelle des Körpers Stössen und anderer Gewalteinwirkung aussetzt.

Die Bursitiden sehen wir meist über dem Olecranon, über der Patella und über der Schulterpartie. Die Peritendinitiden findet man an der Achillessehne, den Beugern und Streckern der Finger, sowie über der Schulterpartie, alles Stellen, die in hohem Grade äusserer Gewalteinwirkung durch Stösse, Schläge u. dgl. ausgesetzt sind oder wo das mechanisch-funktionelle Moment bedeutend ist.

Die Bedeutung dieses mechanisch-funktionellen Momentes für die Lokalisation ist auch in betreff der Arthritiden festzustellen.



Bild 4 A.

A) Ein Fall von Polyarthritis rheumat. chron. mit den proximalen Fingergelenken II und IV der rechten Hand angegriffen. Am Anfang des Prozesses.

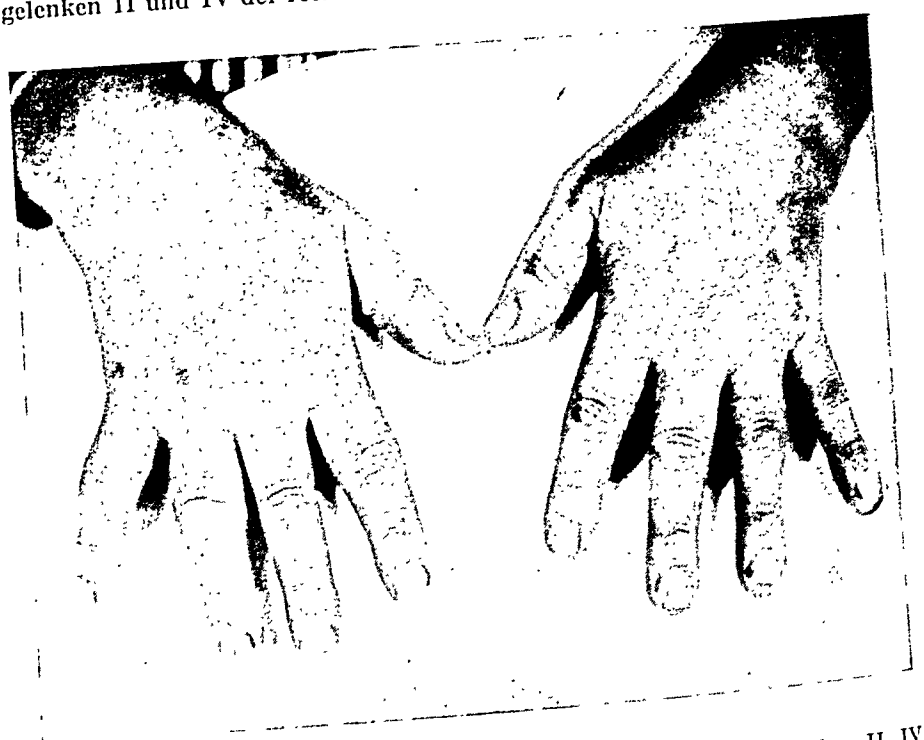


Bild 4 B.

B) Ein ähnlicher frühzeitiger Fall mit den proximalen Fingergelenken II, IV und V, dem Metacarpophalangealgelenk III der rechten Hand angegriffen mit periartikulärem Oedem aber nur erst sehr geringem Oedem am linken IV. proximalen Fingergelenk.

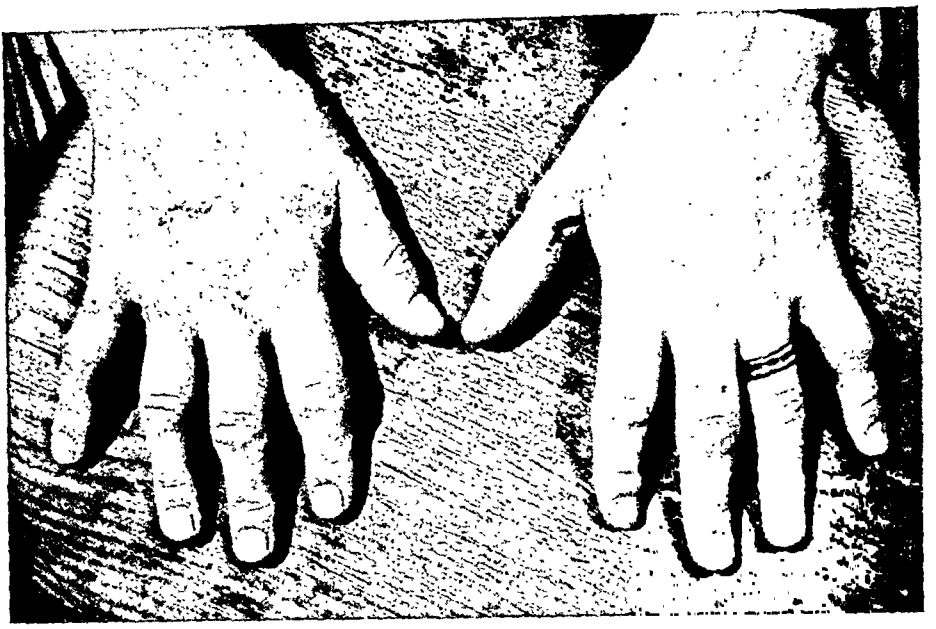


Bild 5.
Ein Fall von Polyarthritis rheumat. chron. mit sämtlichen proximalen Fingergelenken an beiden Händen ausser dem linken Ringfinger angegriffen. Die Frau hat ihre Ringe an diesem Finger immer — auch bei der Arbeit — getragen, und es scheint, als ob dadurch dieser Finger etwas mehr als die übrigen geschützt worden ist.

So kann beispielsweise erwähnt werden, dass wenn bei Polyarthritis rheumat. chron. die ersten schleichenden Gelenkerscheinungen an der häufigsten Prädilektionsstelle, den proximalen Fingergelenken, auftreten, man sie gewöhnlich an einem Gelenk der rechten Hand und zwar am häufigsten am proximalen Gelenk des Zeige, fingers beobachtet. Bisweilen sind beide Zeigefinger angegriffen bevor andere Gelenke erkrankt sind. Bei Linkshändern dagegen werden oft die Finger der linken Hand zuerst angegriffen. Angesichts der Schwierigkeit, bei einem so wechselvollen und bunten Krankheitsbild wie dem rheumatischen überhaupt Regeln aufzustellen, sei dies nur mit Vorbehalt erwähnt.

Ist andererseits ein Gelenk aus irgendeinem Grunde von stärkerer Belastung entbunden, so wird dieses Gelenk oft nicht angegriffen. Ein Beispiel hierfür ist der folgende Fall.

*E. A. V. S. Hausangestellte. 28 Jahre.* 3 Jahre, bevor die Patientin an chronischer rheumatischer Polyarthritis erkrankte, war nach einer *septischen Tendovaginitis der Beugersehne des linken Daumens* durch Narbenbildung der Daumen in extremer Flexionsstellung in der Hand fixiert, wodurch die Funktionstauglichkeit dieser Hand hochgradig gehemmt wurde,



Bild 6.

Die Fingergelenke an der arbeitsuntauglichen linken Hand sind von dem rheumatischen Prozess nicht angegriffen, dagegen diejenigen der rechten Arbeitshand.

so dass sie kaum gebraucht werden konnte. Bei der rheumatischen Erkrankung wurden *u. a. sämtliche proximalen Fingergelenke der rechten Hand angegriffen, während die Gelenke der linken Hand gar nicht befallen wurden* (siehe Abb. 6).

Als ein weiteres Beispiel sei erwähnt, dass sich unter den an der Rheuma-Klinik des Lunder Akad. Krankenhauses behandelten Fällen von Febris rheumatica c. Arthritis chron. und Polyarthritis rheumat. chron., die nachuntersucht wurden und vor allem in dieser Serie Gegenstand der Untersuchung gewesen sind, 4 Fälle befunden haben, wo die betreffenden Patienten *infolge einer früheren Poliomyelitis in einer oder zwei Extremitäten gelähmt waren.* In allen diesen 4 Fällen war *kein Gelenk der gelähmten Extremität bzw. Extremitäten angegriffen.* Einer von diesen Fällen sei hier kurz mitgeteilt.



Bild 7.

*Genua valga* mit Arthritiden in beiden Kniegelenken. Das rechte Knie hat die grösse Valgität und der Rheuma-Prozess zeigt auch da seine grösste Malignität.

*D. S. J. Schneider. 30 Jahre.* Mit 1 ½ Jahren *Poliomyelitis*, seitdem ist die Muskulatur des linken Beines paretisch. — Mit 29 Jahren zweimal, im Abstand von 2 Wochen, akute *Tonsillitis*. 3 Wochen nach der letzten Tonsillitis erkrankte der Patient akut an *Febris rheumatica c. Endocarditis, Myocarditis + Polyarthritis*. Der Prozess zog sich in die Länge, teils in Form einer *Valvulitis* mit nachfolgendem Mitralfehler, teils in Form einer *chronizitierenden Arthritis*, wegen welcher er zweimal 1932—33 in der hiesigen Rheuma-Klinik gelegen hat. Der polyarthritische Prozess war dabei in erster Linie im rechten Kniegelenk und rechten Fussgelenk lokalisiert, während *sämtliche Gelenke des paretischen linken Beines ohne jedes Anzeichen einer Arthritis* waren.

*Ist andererseits ein Gelenk aus irgendeiner Ursache zu einem locus minoris resistentiae geworden, durch unproportionierlich starke*

*Belastung, Gewohnheitstraumata oder einzelne gröbere Gewalteinwirkungen, so wird nicht ganz selten dieses Gelenk vor anderen von einem arthritischen Prozess angegriffen, der teils bedeutend malignerer Art sein und teils bedeutend länger andauern kann als in den übrigen Gelenken.* Ein Beispiel dafür, was eine unrichtige Belastung in diesem Zusammenhang bedeuten kann, bietet der folgende Fall:

*S. A. D. Haushälterin, 50 Jahre. Gewicht 100 kg.* Ausgeprägtes *Genu valgum dx.* Die Patientin erkrankte etwa ein halbes Jahr vor der Aufnahme in die Rheuma-Klinik des Lunder Akad. Krankenhauses schleichend ohne Prodromalsyndrom an chronischer rheumatischer Polyarthritis, die Schulter-, gewisse Finger-, Fuss- und Kniegelenke befiel. Der Prozess ging in sämtlichen Gelenken zurück, nur nicht in den *Kniegelenken*, wo er *im rechten einen besonders malignen Charakter angenommen* hat mit Knochen- und Knorpeldestruktion, weshalb die Patientin in der hiesigen Rheuma-Klinik zur Behandlung kam (siehe Abb. 7).

Das hohe Körpergewicht hatte hier in Verbindung mit der statischen Insuffizienz des rechten Kniegelenkes ein locus minoris resistentiae bewirkt und der rheumatische Gewebsprozess hatte sich hier fixiert.

Ein weiteres Beispiel hierfür ist der Fall eines Rohrleitungsarbeiters, der an einer typischen chronischen rheumatischen Polyarthritis erkrankte, die anfangs mehrere Gelenke angriff. Der Prozess ging auch hier nach einigen Monaten zurück, nur nicht im rechten Schultergelenk, wo er einen malignen, destruktiven Charakter annahm, was allmählich zu einer praktisch völligen Ankylose und Arbeitsunfähigkeit führte. Der Patient hatte in den Jahren vor der Erkrankung bei der Arbeit schwere Rohre u. dgl. auf der rechten Schulter getragen und hatte in diesem rechten Schultergelenk schon bevor er an der rheumatischen Affektion erkrankte, eine deformierende Arthrose, obwohl leichten Typs, gehabt.

*Die Gewohnheitstraumata* hatten also in dem Falle dieses Arbeiters im rechten Schultergelenk ein locus minoris resistentiae geschaffen, wodurch der rheumatische Prozess in diesem Gelenk fixiert wurde.

Dieselben Folgen können natürlich auch *einzelne schwerere Traumata* haben. Unter dem obengenannten Krankengut unserer Klinik aus den Jahren 1928—33 fand sich ein solches mechanischer Art bei 2 Fällen mit Febris rheumatica und bei 5 Fällen mit Polyarthritis rheumat. chron.

Die besagten Fälle werden nachstehend kurz beschrieben.

*K. H. K. Schreiner. 36 Jahre.* Mit 10 Jahren Febris rheumatica. Mit 32 Jahren bei einem Sturz vom Baugerüst *Subluxation des rechten Talocruralgelenks.* Etwa 5 Monate nach dem Unfall akute *Tonsillitis* mit nachfolgender *Febris rheumatica c. Endocarditis + Polyarhritis. Das Polyarthritissyndrom begann im rechten Talocruralgelenk, war hier am hochgradigsten und blieb hier auch am längsten bestehen.* — 3 Jahre später wieder akute *Tonsillitis*, ebenfalls mit nachfolgender *Febris rheumatica c. Endocarditis + Polyarthritis.* Auch bei diesem Ausbruch der Krankheit, der ihn in die hiesige Rheuma-Klinik führte, *begann das Polyarthritissyndrom im rechten Talocruralgelenk, war hier am hochgradigsten und blieb am längsten bestehen.*

*S. G. A. Textilarbeiter. 34 Jahre.* Am 27. 8. 1932 erlitt der Patient einen Unfall bei der Heuernte; dabei *drang eine Heugabel in die Volarseite der rechten Hand und verursachte eine grosse lappige Wunde.* Die Wunde eiterte und es entstand eine eitrige Peritendinitis in der Beugersehne des kleinen Fingers, weshalb er im Krankenhaus des Heimatortes behandelt wurde. Am 20. 10. 32 wurde er von dort relativ geheilt entlassen, erkrankte aber am Tage darauf, 21. 10. 32, akut an einem *akuten Polyarthritissyndrom, zuerst* wurde *das rechte Handgelenk* angegriffen, dann mehrere andere Gelenke. *Der Prozess bestand am längsten im rechten Handgelenk und war hier sowie in ein paar Fingergelenken der rechten Hand besonders malign*, weshalb der Patient in der hiesigen Rheuma-Klinik war.

*G. I. G. Landarbeiter. 18 Jahre.* Mit 15 Jahren sprang der Patient über einen Zaun, *rutschte aus und traf mit geraden Knien auf, die sich überstreckten.* Er hatte äusserst starke Schmerzen und musste sich hinlegen. Nachmittags ging es ihm jedoch besser, so dass er wieder aufstehen konnte. *2 Tage später begannen die Kniegelenke zu schmerzen und leicht anzuschwellen*, und einige Tage später traten verstärkte Schwellung und Bewegungsschmerzen sowie Fieber auf, weshalb er sich zu Bett legen musste. Der herbeigeholte Arzt sagte, der Patient habe *Gelenkrheumatismus.* Nach 4monatiger Bettlägerigkeit war er wieder gesund.

*Zwei Jahre später* traten die gleichen Symptome erneut auf und der Patient lag unter der Diagnose der *chronischen rheumatischen Polyartritis* in der hiesigen Rheuma-Klinik. *Allein die Kniegelenke waren angegriffen*, und zwar war der Prozess hier recht malign. Doch war der Patient nach einigen Monaten völlig wiederhergestellt.

*K. M. B. Bautischler. 41 Jahre.* Am 22. 7. 1929 sprang der Patient von einem 1 ½ m hohen Baugerüst herunter und *verrenkte sich dabei das rechte Talocruralgelenk*, welches stark anschwoll. *Die Schwellung ging indessen nicht zurück*, und am 15. 8. 29 — also *nach etwa 3 Wochen — trat schleichend eine Anschwellung auch mehrerer anderer Gelenke auf, verbunden mit Fieber.* Der S. R.-Wert wurde am 15. 8. 29 mit etwa 70 mm/1 Stde ermittelt. Die Diagnose lautete auf *chronischen Gelenkrheumatismus*, und der Pat. kam deswegen nach einiger Zeit in die hiesige Rheuma-Klinik. *Der Prozess war im rechten Talocruralgelenk am malignsten und blieb hier die längste Zeit bestehen.*

*F. N. P. Elektriker. 45 Jahre. Mit 42 Jahren* fiel dem Patienten *durch Unfall ein schwerer Stamm aufs linke Kniegelenk.* Gleich danach *schwoll das Kniegelenk stark an.* Die Schwellung wurde zunächst als direkte Folge des Unfalls aufgefasst, doch *blieb sie 3 Monate lang bestehen,* bei hohen S.R.-Werten und subfebriler Temperatur, weshalb die Diagnose im Krankenhaus des Heimatortes, wo er lag, auf *chronischen Gelenkrheumatismus* lautete. Nach einem halben Jahr war der Patient wieder hergestellt. *3 Jahre später erkrankte er erneut:* Schwellung und Bewegungsschmerzen zuerst im linken Kniegelenk, dann im rechten Kniegelenk und schliesslich in mehreren anderen Gelenken. Der Kranke lag bei dieser Gelegenheit unter der Diagnose Polyarthritis rheumat. chron. in der hiesigen Rheuma-Klinik. *Der Prozess war am malignsten im linken Kniegelenk,* wo er auch Knochen- und Knorpeldestruktion verursachte, denen später reaktive Auflagerungen folgten; es blieb bei der Ausheilung eine leichte Kontraktur zurück.

*J. S. T. S. Landarbeiter. 42 Jahre. Mit 30 Jahren* stürzte der Patient mit dem Fahrrad und *verstauchte sich das rechte Handgelenk. Das Gelenk war daraufhin mehrere Monate lang geschwollen und schmerzhaft. 2 Jahre später* ein halbes Jahr lang *dieselben Beschwerden* seitens des gleichen Gelenks ohne äussere Ursache. Der Patient suchte damals keinen Arzt auf. *Nach weiteren 8 Jahren* begannen wiederum *dieselben Beschwerden seitens dieses rechten Handgelenks.* Jetzt traten nach einigen Monaten gleichsinnige Beschwerden im linken Handgelenk auf, und nach und nach wurden mehrere Extremitätengelenke in gleicher Weise angegriffen. Ein Arzt stellte Gelenkrheumatismus fest und wies den Kranken in die hiesige Rheuma-Klinik ein. Es bestand eine *äusserst maligne chronische rheumatische Polyarthritis mit Destruktion des Knochens und Knorpels beider Carpi,* doch war *der rechte Carpus am schwersten angegriffen.* Die übrigen Gelenke waren weniger angegriffen.

*E. V. N. Haushälterin. 47 Jahre. Mit 39 Jahren* blieb sie mit dem Schuh in einer Gleisschiene hängen und *verstauchte sich das linke Talocruralgelenk Mit 45 Jahren* erlitt die Frau einen Unfall, wobei das *linke Talocruralgelenk* abermals eine *Distorsion* erfuhr. *Mit 47 Jahren schwoll nach einem langen Marsch in tiefem, losem Sand das linke Talocruralgelenk wieder an,* gleichzeitig hatte sie Fieber, der herbeigeholte Arzt sagte, sie habe *Gelenkrheumatismus* und verordnete Bettruhe. Indessen trat keine Besserung ein, sondern nach ein paar Wochen begann auch das rechte Talocruralgelenk anzuschwellen, dann folgte das eine Gelenk nach dem andern, weshalb die Patientin in die hiesige Rheuma-Klinik eingewiesen wurde. *Es bestand ein chronisches Polyarthritissyndrom, am malignsten im linken Talocruralgelenk, wo eine beginnende Knochen- und Knorpeldestruktion sowie leichte reaktive Veränderungen festzustellen waren. Der Prozess blieb in diesem Gelenk am längsten bestehen und hinterliess eine leichte Kontraktur.*

In allen diesen Fällen war es ziemlich wahrscheinlich so, dass *das Trauma ein locus minoris resistentiae geschaffen hat, wodurch der*

*rheumatische Prozess in dem bzw. den betreffenden früher geschädigten Gelenken fixiert worden ist.* Der Prozess nimmt an der besagten Stelle einen weit maligneren Charakter an als in den übrigen Gelenken. Schwieriger zu entscheiden ist hingegen die Frage, ob das Trauma in diesen Fällen etwa sozusagen als das den rheumatischen Krankheitsprozess auslösende Moment anzusprechen ist.

Bei den ersten beiden Fällen von Febris rheumatica c. Arthritis chron. kommt gleichzeitig ein infektiöses Moment hinzu, das ebenfalls in dem hyperergischen Organismus als auslösendes Moment gewirkt haben kann. Entsprechende Fälle aus der hiesigen Medizinischen Klinik, über die früher berichtet worden ist (Acta Med. Scand. 88. 342. 1936), sind in dieser Beziehung reiner und etwas eindeutiger.

Bei den 5 letzteren Fällen, wo ausnahmslos ein chronischer arthritischer Prozess in direktem Anschluss an das Trauma und zwar zuerst in dem verletzten Gelenk auftrat, war die differentialdiagnostische Entscheidung, ob eine Distorsion oder ein arthritischer Prozess vorlag, in sämtlichen Fällen im Anfang sehr schwer. Erst das Auftreten allgemeiner Infektionserscheinungen seitens des Organismus sowie ausgedehnterer arthritischer Prozesse sicherte die Diagnose. Die besagten Fälle sind alle ziemlich gleichgelagert, und man kann hier sagen, dass das Trauma in sämtlichen Fällen das auslösende Moment gewesen zu sein scheint, durch welches die ersten arthritischen Erscheinungen ausgelöst wurden. Ähnliche Fälle sind u. a. von Engström und v. Koch beschrieben worden.

Die Bedingungen, die man vom versicherungstechnischen Gesichtspunkt aus aufstellen könnte, um in solchen Fällen einen möglichen Zusammenhang anzuerkennen, nämlich

1) dass der Krankheitssymptomenkomplex in unmittelbarem Zusammenhang mit dem Trauma, längstens nach Verlauf einiger Tage begonnen haben muss,

2) dass die Krankheitserscheinungen zuerst in dem der Gewalteinwirkung ausgesetzten Gelenk aufgetreten sein müssen,

3) dass der Patient unmittelbar nach dem Trauma zu arbeiten aufgehört hat,

4) dass vor dem Trauma keine Polyarthritissymptome bestanden haben dürfen,

sind in allen diesen 5 Fällen von chronischer Arthritis erfüllt. Indessen kann man auch andere Krankengeschichten vorfinden,

ausgelöst hatte, wie es früher u. a. von Gudzent, Klinge, Miltner, Hu u. Fang u. a. gezeigt worden ist, nämlich durch eine gröbere mechanische Gewalt gegen ein grösseres Gelenk, aufzeigen können, dass das Trauma an und für sich gewöhnlich nicht unmittelbar so starke Gewebsveränderungen bewirkt. Bei Traumata von der Stärke, wie sie hier in Frage kommt, werden weder Knochen noch Knorpel verletzt, sondern nur die Weichteile. Es zeigt sich indessen, dass die für die Zukunft wichtigen Folgen dadurch entstehen, dass die periartikulären Gefässe verletzt werden, worunter die Nutrition gewisser Teile leidet, vor allem die Nutrition des in dieser Hinsicht so empfindlichen Knorpels mit seiner relativ spärlichen Vaskularisation, und dass es auf diese Weise dort später zu intracartilaginösen Veränderungen kommt. Die ursprünglich auch in diesem Gelenk ebenso wie in den übrigen Gelenken des Versuchstieres verhältnismässig leichte Synovitis verwandelt sich auf diese Weise nach einiger Zeit zu einer bedeutend ernsteren destruktiven Arthritis. Und in der Folge können sich reaktive Auflagerungen bilden, wodurch es zu einem sekundären Arthrosebild kommt, gerade wie wir es oben bei mehreren unserer klinischen Fälle sahen. Das klinische Schema ist hier, wie schon oben in den Krankengeschichten klargestellt wurde, meistens das folgende: *Synovitis → destruktive Arthritis → sekundäre Arthrose.*

Dieser Prozess begnügt sich indessen nicht nur mit diesen Erscheinungen seitens des Gelenkes, sondern daneben haben wir hier meistens in den umgebenden Skeletteilen eine fleckförmige und diffuse Kalkatrophie im Sinne Sudeck's — ein Prozess, wie man ihn ja oft in den vorgeschritteneren Fällen der chronischen rheumatischen Polyarthritis sieht. In ein paar derartigen Fällen, die zur Sektion kamen, konnte indessen Jaffe zeigen, dass diese Kalkatrophie, soweit es sich nach den Sektionsbefunden beurteilen lässt, auf einem verstärkten Kalkstoffwechsel beruht — was ja mit der klinischen Erfahrung unserer Klinik im Einklang steht, dass diese Fälle mit einem verhältnismässig hohen Serumkalkspiegel einhergehen — zwischen 11 und 13 mg % — was seinerseits auf einer Hypervaskularisation dieser Gewebe beruhen soll, und zwar besonders des kortikalen Knochens, die nach Jaffe's Ansicht mit dem früher erlittenen Trauma und den dadurch hervorgerufenen Gewebsschäden zusammenhängen können. Dagegen lässt sich jedoch einwenden, dass diese diffuse und fleckförmige Kalkatrophie

ein ziemlich allgemein bei diesen chronischen rheumatischen Polyarthritiden begegnender klinischer Zug ist, unabhängig davon, ob die Vorgeschichte ein Trauma verzeichnet oder nicht. Das Trauma ist deshalb sicherlich nicht die Ursache der von Jaffe beobachteten veränderten Vaskularisation, vielmehr hat diese andere Ursachen. Jedenfalls aber sind die *Jaffe'schen* Befunde äusserst interessant, denn früher vermochte man nicht recht zu erklären, wie es kommen kann, dass der Kalkspiegel im Serum bei diesen Fällen mit relativ schlechter und verlangsamter peripherer Zirkulation so hoch sein kann (siehe Acta Med. Scand. 103. 88. 1940).

Dieser diffuse und fleckförmige Kalkschwund in grossen Teilen der umgebenden Knochen ist ja auch das charakteristischste Symptom in dem klinischen Bilde, das namentlich französische Autoren wie Leriche, Weissenbach und Francon unter dem Namen der *posttraumatischen osteoporotischen Arthritis* geschaffen haben, und bei dem es sich um ein nach einem Trauma verschiedener Art aufgetretenes Arthritissyndrom mit starkem periartikulärem Ödem und anderen örtlichen entzündlichen Zeichen, daneben aber auch allgemeinen Symptomen in Form von Fieber usw. handelt, Symptome, die in keinem logischen Verhältnis zur Stärke des ursprünglichen Traumas stehen. Es fragt sich indessen, ob das besagte Krankheitsbild wirklich selbständig ist, ob es sich in diesen Fällen wirklich um Krankheitsbilder von anderer Art als die hier besprochenen posttraumatischen rheumatischen oder hyperergischen Krankheitsbilder handelt. Nach der klinischen Beschreibung der Fälle zu urteilen, wie sie besonders Weissenbach und Francon gegeben haben, scheint nämlich das ganze Krankheitsbild von dem hyperergischen Typus zu sein, der hier als einer der wesentlicheren Züge im Bilde der rheumatischen Krankheit aufgefasst wird, und man kann kaum behaupten, dass diese französischen Autoren eine haltbare differentialdiagnostische Abgrenzung gegenüber den rheumatischen Arthritiden erbracht hätten.

Sollte wirklich diese posttraumatische osteoporotische Arthritis als selbständiges Krankheitsbild existieren, so dürften sämtliche 5 oben zuletzt beschriebenen Fälle, bei denen auf das mechanische Trauma eine chronische Arthritis gefolgt ist, als Fälle derselben anzusprechen sein.

Bei der Diskussion dieser posttraumatischen rheumatischen oder hyperergischen Zustände kann man auch nicht umhin, Stel-

lung zu einem Bilde von Swift zu nehmen, das kürzlich von Collins veröffentlicht worden ist. Dieses Bild zeigt eine Anhäufung von Rundzellen wie bei dem rheumatischen Gewebsschaden in einem Synovialknötchen in einem Falle von chronischer traumatischer Tendosynovitis, der den obengenannten Fällen der französischen Autoren gleicht. Nun haben Fischer u. a. das Typische des Gewebsschadens bei diesen chronischen rheumatischen Polyarthritis teils in Gebieten fibrinoider Degeneration gesehen, die von einem Kranz von Fibroblasten umgeben sind wie bei den ersten Stadien der rheumatischen Gewebsschädigung bei Febris rheumatica, teils in grossen follikelähnlichen Häufungen von Lymphocyten und Plasmazellen von einem Typus, wie wir ihn oft in etwas vorgeschritteneren Stadien der Febris rheumatica sehen. Im Gegensatz zu diesen Autoren steht nun Collins auf dem Standpunkt, dass keine dieser Veränderungen spezifischen Charakters ist; nach ihm entsteht die fibrinogene Schwellung des kollagenen Bindegewebes unter dem Einfluss gewisser auch nicht spezifischer Reizmittel, einerlei, ob das Gewebe hyperergisch ist oder nicht, und die grossen Rundzellenanhäufungen stellen nach Collins die nicht spezifische Synovialreaktion gegenüber jeder chronischen Infektion dar. Letzteres kann möglicherweise zutreffen, obwohl man kaum behaupten kann, dass Collins dies bewiesen hätte. Dass die erste Hälfte seiner Behauptung richtig wäre, ist jedoch weniger wahrscheinlich, und der Beweis, den er für die Richtigkeit seiner Ansicht anzieht, nämlich das besagte Bild von Swift, ist kein Beweis. Was stände dem im Wege, dass es sich in diesem Falle gerade um einen Fall des posttraumatischen rheumatischen oder hyperergischen Typs gehandelt hat, der oben durch Beispiele belegt wurde, wo gerade das Trauma das für die Auslösung des rheumatischen Krankheitsbildes entscheidende Moment gewesen ist.

Nach meinem Erachten sprechen die oben angeführten klinischen Beispiele mehr dafür, dass *das mechanische Trauma wirklich auslösendes Parallergen bei rheumatischen Krankheitsbildern sein kann*, entsprechend wie Gudzent, Klinge u. a. hyperergische Arthritiden im Tierversuch mit einem Bilde auszulösen vermochten, das durchaus mit dem bei den rheumatischen Arthritiden des Menschen übereinstimmt, und zwar indem sie das allergisierte Tier gröberer Gewalt gegen ein grösseres Gelenk aussetzten bzw. ein grösseres Gelenk einer schwereren Anstrengung unterzogen.

Diese hyperergischen Gewebsschäden der Versuchstiere lassen sich jedoch auch durch stärkere Anstrengungen anderer Organe als der Gelenke auslösen. So gelang es z. B. Knepper u. Waaler, bei sensibilisierten Kaninchen hyperergische Gewebsveränderungen des Herzens und gewisser gröberer Arterien dadurch hervorzurufen, dass sie die Tiere sehr stark bewegten, was eine entsprechend heftige Herztätigkeit auslöste. In diesem Falle waren es das Herz und die gröberen Gefässe, besonders die gröberen Lungenarterien, die einer funktionellen Überbelastung ausgesetzt wurden, wodurch dort die hyperergischen Gewebsschäden entstanden.

Gleichsinnige Befunde in der Klinik sind möglicherweise die Fälle von Herzschäden nach äusserer Gewalteinwirkung, wie sie von Ahlberg, Warburg u. a. beschrieben worden sind.

Eine Erklärung dafür, wie das Trauma in diesen Fällen als Parallergen wirkt, hat Whitfield zu geben versucht. Er meinte zeigen zu können, dass nach einer Läsion oder einem anderen Schaden an einem Körpergewebe durch autolytische oder degenerative Veränderungen körpereigene Stoffe in den versehrten Geweben zu anderen Stoffen körperfremden Charakters umgewandelt werden. Ein solcher Stoff kann dann das auslösende Moment für einen hyperergischen Krankheitsprozess sein. Als Beispiel führt Whitfield an, er habe in einem Falle zehn Tage nach einer stumpfen Gewalt gegen die Körperfläche eines Patienten, bei der die Haut unversehrt blieb, jedoch subkutane Blutungen entstanden, ein erythematös-urtikarielles Exanthem beobachtet, wie man es oft bei Serumkranken sieht.

Prinzipiell ist dies ja vor allem versicherungstechnisch von sehr grosser Bedeutung, denn durch eine solche Erklärung stellt sich ja der etwaige Kausalzusammenhang zwischen einem Trauma und einem nachfolgenden hyperergischen Krankheitsprozess, mag dieser nun rheumatischer Natur sein oder nicht, klarer dar. Zwischen post und propter in solchen Fällen zu unterscheiden, ist natürlich stets schwierig, dem Verf. erscheint es aber doch als eine Realität, dass ein Trauma das auslösende Moment einer Polyarthritis sein kann, mag die Erklärung dafür nun die von Whitfield angegebene oder eine andere sein.

* * *

Es zeigt sich indessen, dass man in diesen Tierversuchen die hyperergische Gewebsschädigung auch auf andere Weise auslösen kann, in erster Linie durch ein *thermisches Trauma* statt eines mechanischen. Statt die Gelenke durch Schläge zu beeinflussen, statt die Tiere vom Tisch herunterspringen zu lassen, kann man die hyperergische Arthritis auch dadurch auslösen, dass man das Gelenk stark abkühlt. Bruun, Klinge, Vaubel, Yasukawa u. a. haben auf diesem Wege ebenso schöne hyperergische Arthritiden bei Ratten sowohl als bei Kaninchen und Affen hervorrufen können wie mittels der vorerwähnten mechanischen Gewalteinwirkung.

In der Klinik ist es ebenso. *Ebenso wie das mechanische Trauma in gewissen Fällen das Moment zu sein scheint, welches das rheumatische Krankheitsbild auslöst, begegnen wir auch Fällen, und zwar ebensooft, bei denen ein entsprechendes thermisches Trauma dieselbe Bedeutung gehabt zu haben scheint.*

Unter dem obengenannten Krankengut der hiesigen Klinik aus den Jahren 1928—33 finden wir auch 6 solche Fälle, die nachstehend in aller Kürze angeführt seien.

*J. L. J. Hausangestellte. 24 Jahre.* Mit 24 Jahren musste die Patientin am 1. 3. 30 bei 20° Kälte an einer offenen Haltestelle über eine Stunde auf den Zug warten und *fror* dabei *entsetzlich an den Füssen. Am nächsten Tage erkrankte die Patientin an einem akuten Polyarthritissyndrom* mit hohem Fieber, Kapselschwellung und Bewegungsschmerzen im *rechten Fussgelenk.* Einen Tag später war auch das *linke Fussgelenk* angegriffen und nach und nach wurden mehrere Extremitätengelenke befallen. Die Kranke lag dann unter der Diagnose *Febris rheumatica c. Endocarditis, Myocarditis, Nepritis + Polyarthritis* in der hiesigen Rheuma-Klinik. *Das Gelenksyndrom war in den Fussgelenken klinisch am malignsten und blieb hier am längsten bestehen.*

*E. D. T. Hausangestellte. 33 Jahre.* In dem Haushalt auf dem Lande, in welchem die Patientin angestellt war, besorgte sie in den Tagen *27. 2.— — 1. 3. 33* die sog. grosse Wäsche und *wusch* dabei *in der Winterkälte (zwischen —12° C und —15° C) im Freien in eiskaltem Wasser. Am Tage darauf,* am 2. 3. 33, *erkrankte sie an einem akuten Polyarthritissyndrom* mit hohem Fieber, Anschwellung und Bewegungsschmerzen in den Handgelenken. Nach einigen Tagen wurden mehrere andere Gelenke angegriffen, und die Patientin lag dann in der hiesigen Rheuma-Klinik unter der Diagnose *Febris rheumatica c. Polyarthritis chron. Die Gelenksymptome waren klinisch in den Handgelenken am ausgeprägtesten und hielten hier auch am längsten an.*

*H. J. K. J. Bauernfrau. 43 Jahre. Ende Nov. 1928 wusch die Patientin im Freien* und spülte bei dieser Gelegenheit die Wäsche in kaltem Wasser.

Die Wäsche dauerte 2 Tage. *2 Tage später begannen die Handgelenke zu schmerzen*, sonst bemerkte sie erst nichts, doch nach einigen Tagen begannen diese Gelenke anzuschwellen und die Schwellung nahm in den folgenden Wochen zu. Nach 4 Wochen bekam sie leichtes Fieber, ging zum Arzt und lag dann etwa 2 Wochen zu Bett. Nach einer eiwa 2 Monate währenden Besserung trat wieder leichtes Fieber ein und die Symptome seitens der Handgelenke verschlimmerten sich, ausserdem wurden jetzt auch die Finger- und verschiedene andere Gelenke in gleicher Weise angegriffen. Die Frau lag dann in der hiesigen Rheuma-Klinik unter der Diagnose *Polyarthritis rheumat. chron. Die Gelenksymptome blieben in den Handgelenken am längsten bestehen und waren hier am ausgeprägsten.*

*7 Jahre später* bekam sie ein *Rezidiv* des chronischen Gelenkrheumatismus, diesmal verursachten die Hüftgelenke die stärksten Beschwerden. *Diesmal hatte sie unmittelbar vor Ausbruch der Krankheit eine ganze Woche gebacken und dabei fast dauernd stehen müssen.* Sie bekam bei dieser Arbeit starke Schmerzen in den *Hüftgelenken*, die nicht verschwanden, sondern nach etwa 2 Wochen in das rheumatische Krankheitsbild mit Fieber und Beschwerden seitens mehrerer Gelenke übergingen. Auch diesmal gesundete sie. Keine Zeichen von Arthrosen.

*D. C. S. Möbelschreiner. 40 Jahre. Anfang Febr. 1930* beteiligte sich der Patient als Mitglied der freiwilligen Ortsfeuerwehr am *Löschen eines grossen Brandes*. Bei den Löscharbeiten wurden *der rechte Arm und die Schulter mit eiskaltem Wasser völlig durchnässt. 10 Tage später* traten ziemlich plötzlich *Bewegungsschmerzen im rechten Schultergelenk* auf, am Tage darauf leichtes Fieber und schwerere Schmerzen, dann ein paar Tage lang eine gewisse Besserung. Etwa 4 Wochen nach dem Brande begann das rechte Ellbogengelenk anzuschwellen und zu schmerzen, etwa 6 Wochen nach dem Brande traten dieselben Symptome auch in den proximalen Fingergelenken beider Hände auf. Ein Arzt schickte ihn in die hiesige Rheuma-Klinik, wo er dann unter der Diagnose *Polyarthritis rheumat. chron.* lag. Er hatte einen sehr malignen Prozess mit Arthritiden destruktiven Typs in mehreren Gelenken, Peritendinitiden, Bursitiden, subkutanen Noduli und wurde allmählich Invalide mit starker Destruktion mehrerer Gelenke, *am hochgradigsten war die Destruktion im rechten Ellbogengelenk.*

*J. A. M. O. Arbeiterfrau. 44 Jahre. Am 18. 11. 20 wusch und spülte die Patientin den ganzen Tag im Freien in kaltem fliessendem Wasser. Am nächsten Tage heftige Arthritisbeschwerden in den Handgelenken* und Fieber, einige Tage später wurden auch mehrere andere Gelenke angegriffen. Erst nach einem halben Jahre war sie wieder gesund. 1928 und 1929 traten die Gelenkbeschwerden mit der Zeit erneut auf, zuerst in Hand- und Fingergelenken, allmählich in den meisten Extremitätengelenken. Sie lag in der hiesigen Rheuma-Klinik und wurde allmählich völlig wiederhergestellt. *Hand- und Fingergelenke waren am stärksten angegriffen*, doch traten keine destruktiven Arthritiden auf.

*A. E. T. Arbeiterfrau. 29 Jahre.* Mit 16 Jahren arthritische Beschwerden in den Kniegelenken, die nach einem halben Jahr gänzlich verschwanden. *Ende Juli 1927 im Alter von 24 Jahren anstrengende Wäsche und Spü-*

*len in kaltem Brunnenwasser. 2 Tage später schmerzten Hand- und Fingergelenke stark und schwollen mässig an.* Die Beschwerden nahmen zu, und nach ein paar Wochen wurden auch andere Gelenke angegriffen und die Patientin bekam Fieber. Sie wurde in der hiesigen Med. Klinik behandelt und war nach einigen Monaten wiederhergestellt.

*Im Alter von 29 Jahren, Febr. 1932, war die Patientin eines Tages bei tiefem Schnee lange draussen und wurde nass und kalt an Füssen und Knien. Am nächsten Tage waren die Kniegelenke steif, geschwollen und schmerzhaft.* In den folgenden Wochen entwickelte sich allmählich ein chronisches Arthritissyndrom in mehreren Gelenken, weshalb die Patientin in die hiesige Rheuma-Klinik kam. Nach zeitweiliger Besserung nahm der Prozess allmählich in Knie- und Fussgelenken einen destruktiven Charakter an und machte die Patientin zur Invalidin.

In allen diesen Fällen ist ein thermisches Trauma zu verzeichnen, nach welchem der rheumatische Prozess zur Entwicklung kam. Auch hier scheint das thermische Trauma teils ein locus minoris resistentiae geschaffen zu haben, das den rheumatischen Prozess fixiert und ihm in einem Teil der Fälle in dem oder den vom Trauma getroffenen Gelenken einen maligneren Charakter als in den übrigen Gelenken gegeben hat, teils aber scheint das thermische Trauma in den meisten dieser Fälle auch das auslösende *Parallergen* gewesen zu sein, im gleichen Sinne, wie es oben in bezug auf das mechanische Trauma dargestellt wurde.

Dass diese Rheumakranken in sehr hohem Grade auf pathologische Weise gegenüber Abkühlung ebenso wie gegenüber mechanischen Insulten empfindlich sind, hat klinisch auf verschiedene Weise festgestellt werden können. Eine solche ist die sog. *Buchstab'sche Probe.* Ein sehr interessanter Fall mit pathologischer Reaktion nach der Buchstabschen Probe haben wir neulich in der Klinik gehabt. Ein paar Stunden nach der Abkühlung bekam der 29-jährige Patient eine typische Kälte-Urticaria mit genau derselben Ausbreitung wie die Aetherdusche herumgereicht hatte. Diese Urticaria ging erst am zweiten Tag zurück. Gleichz itig transitorische Eosinophilie (5 %).

*Das thermische Trauma scheint also ebenso wie das mechanische bei rheumatischen Krankheitszuständen als Parallergen dienen zu können,* und als Stütze dieser Auffassung lassen sich nicht nur tierexperimentelle Untersuchungen, sondern auch klinische Befunde beibringen.

## Zusammenfassung.

Das morphologische Bild der rheumatischen Gewebsschädigung ändert sich je nach der mechanisch-funktionellen Belastung der Gewebe in dem Sinne, dass die proliferative Komponente zunehmend überwiegt, je intensiver diese Belastung ist.

Diese mechanisch-funktionelle Beeinflussung lässt sich auch in der Klinik beobachten: Im Herzen werden am stärksten die Klappen der arteriellen Herzhälfte angegriffen; die subkutanen Noduli treten an Stellen auf, die Stössen und Gewalt ausgesetzt sind, ebenso die Bursitiden; die Peritendinitiden und Arthritiden sieht man vornehmlich in den Sehnenscheiden und Gelenken, welche die stärkste mechanischfunktionelle Belastung auszuhalten haben.

Es werden klinische Beispiele dafür angeführt. Die Gelenke einer Hand, die infolge einer Verletzung nicht gebraucht werden kann, werden nicht von dem rheumatischen Prozess angegriffen, ebenso nicht die Gelenke paretischer Extremitäten. Bei Rechtshändern beginnt der Prozess oft damit, dass die Fingergelenke der rechten Hand angegriffen werden, während bei Linkshändern dagegen oft die entsprechenden Gelenke der linken Hand zuerst angegriffen werden. Wird ein Gelenk unverhältnismässig grosser Belastung, Gewohnheitstraumata oder einzelnen schwereren Traumata ausgesetzt, so wird der rheumatische Prozess sozusagen leicht in dieser Lokalisation fixiert und ist an dieser Stelle leicht malignerer Art als in den übrigen Gelenken. Aber das *mechanische* Trauma kann dabei auch hier als auslösendes Parallergen auf den hyperergischen Organismus betrachtet werden.

Entsprechendes gilt auch von dem *thermischen* Trauma, das ebenfalls unter gleichsinnigen Verhältnissen als auslösendes Parallergen betrachtet werden kann, wie hier mitgeteilte klinische Krankengeschichten beleuchten.

### Literatur.

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# Über Schmerzhafte Insuffizienzzustände im Halse.

Von

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Schmerzzustände in der Nackenregion sind recht gewöhnlich und von sehr verschiedenartiger Ätiologie. Die wichtigsten Krankheiten, welche solche Beschwerden verursachen, sind: Spondylosis deformans und deren Vorstadien mit Veränderungen in den Intervertebralscheiben, spezifische sowie unspezifische Entzündungen der Wirbelsäule oder deren Umgebung, Geschwülste, Traumen mit Frakturen oder Luxationen und andere Verletzungen verschiedener Art, Polyarthritis rheumatica, Muskelrheumatismus, Ostitis fibrosa, Osteoporose samt Verkrümmungen der Wirbelsäule, häufig in Form von Skoliosen. Ferner sollen gemäss Mithefer (1934) Sinusiten, Tonsilliten und Zahnentzündungen Anlass zu gesteigertem Muskeltonus in der Halsregion geben können, mit Schmerzen als Folge.

Während meiner Tätigkeit in Bad Sätra Brunn, in den Sommermonaten 1940 und 1941, kamen viele Fälle mit Nackenbeschwerden vor. Die Untersuchung ergab, dass die Ursache der Schmerzen meistens in einer der soeben genannten Krankheiten zu finden war. In 16 Fällen (darunter 12 Frauen) konnte indessen eine Erklärung für die Leiden nicht gefunden werden.

Alle diese 16 Patienten klagten über bohrenden Schmerz in der mittleren und unteren Nackenregion, der oft zum Hinter-

kopf hinauf strahlte. Bei tiefer Betastung fühlten die Patienten leichten bis mässigen Schmerz beiderseits der Spinalfortsätze, zeigten aber keine Empfindlichkeit über den Kanten des Trapezius oder über Mm. sternocleidomast. Die Patienten hielten den Kopf etwas steif und gewöhnlich leicht vorgeschoben. Keiner dieser Fälle wurde unter der Diagnose Muskelrheumatismus gepflegt. Die Senkungsreaktion und der Hämoglobingehalt waren



Fig. 1. Einer der 16 Patienten (D. D. ♀ 31 Jahre alt) in aufrechter Stellung. Die Halswirbelsäule zeigt die charakteristische Formveränderung.

überall normal. Keiner litt an irgendeiner Krankheit, die einen wahrscheinlichen Einfluss auf die vorhandenen Halsbeschwerden haben konnte. Bei der Untersuchung mittelst Röntgendurchleuchtung in Normalstellung der Patienten zeigte es sich, dass alle eine Halswirbelsäule hatten, deren Form wesentlich von der einer normalen abwich. Diese war von $C_7$ bis hinauf einschliesslich $C_4$ fast gerade und innerhalb dieser Partie schräg kranial-ventral gerichtet. Die mangelnde Lordose wurde durch eine kräftige solche an den zwischen kranial von $C_4$ und der Schädelbasis liegenden

Wirbeln ausgeglichen. Bei Ermahnung des Patienten, den Kopf vorwärts oder rückwärts zu beugen, geschah diese Bewegung hauptsächlich kranial um $C_4$. Eine pathologische Skoliose war in der Wirbelsäule nicht vorhanden (s. Fig. 1, 2 u. 3).

Ich habe in der Literatur keine Beschreibung von Schmerzzuständen in der Nackenregion finden können, die eine ähnliche Deformität der Halswirbelsäule aufwies, weshalb ich es für be-



Fig. 2. Derselbe Patient wie in Fig. 1. Aufnahme, nachdem Pat. ermahnt wurde, Kopf und Hals maximal nach hinten zu beugen. Vor Beginn der Behandlung.

gründet halte, in Kürze über diese, meines Erachtens ziemlich isolierte Krankheit zu berichten.

Da kein Verfasser diese Frage früher behandelt hat, ist die Anzahl der in diesem Aufsatz referierten Schriften sehr gering. In meinem Literaturverzeichnis habe ich die wichtigsten Arbeiten aufgenommen, welche Gebiete berühren, die an den hier geschilderten Krankheitszustand grenzen.

Es erscheint vielleicht eigentümlich, dass man an einem relativ geringen Patientmaterial, wie das von mir in Sätra Brunn unter

zwei Sommern behandelte (ca 600), eine so grosse Anzahl Fälle von einer solchen Halsdeformität hat finden können, ohne dass die Literatur dergleichen aufzuweisen hat. Die Erklärung hierfür dürfte darin liegen, dass eine sichere Diagnose nur durch Röntgenuntersuchung der Patienten erreicht werden kann. Dies muss teils mittelst Röntgenphotographierung *in Normalstellung* geschehen, teils mittelst Röntgendurchleuchtung, um die Bewegungen der



Fig. 3. Derselbe Patient wie in Fig. 1 u. 2. Aufnahme, nachdem Pat. ermahnt wurde, Kopf und Hals maximal nach vorn zu beugen. Vor Beginn der Behandlung.

Halswirbelsäule in der Sagittalebene bei aufrechter Stellung kontrollieren zu können. Liegend erhält man nämlich die charakteristische Deformität nicht so typisch beim Kranken. Normale Individuen dagegen zeigen eine für Normalbelastung der Wirbelsäule unphysiologische Form derselben, eine Form, die der oben beschriebenen Abweichung täuschend ähnlich sein kann.

Da ich der Meinung bin, dass die vorliegende Formveränderung der Halswirbelsäule auf einem Insuffizienzzustand beruht, soll hier in aller Kürze über die normalen Belastungsverhältnisse innerhalb dieses Teiles der Wirbelsäule berichtet werden.

Die Halswirbelsäule zeigt in normalem Zustande eine gleichmässig lordotische Beugung. Die oberen und unteren Flächen des letzten Halswirbels neigen schräg kaudal-ventralwärts. Diese Neigung nimmt in kranialer Richtung allmählich ab, so dass $C_3$ gewöhnlich horizontal steht. Die Lordose setzt auch oberhalb $C_3$ fort, weshalb der Atlas nach hinten unten zu gerichtet wird. Die

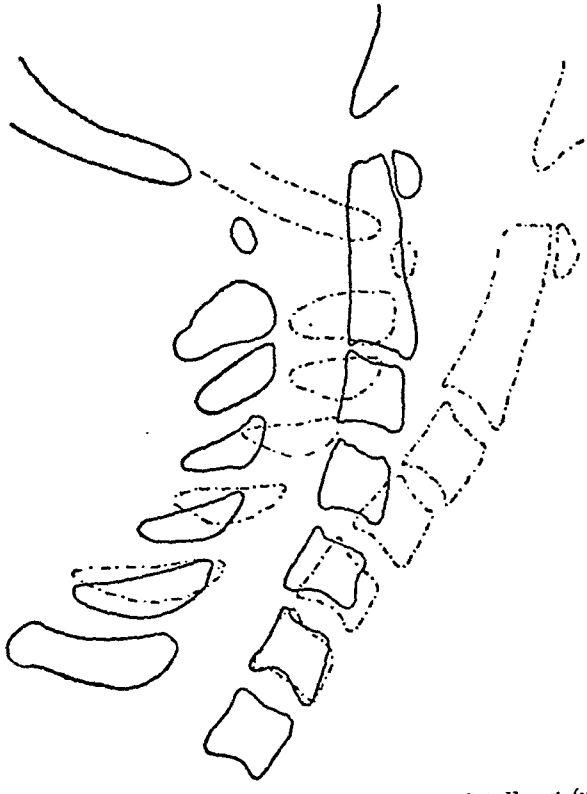


Fig. 4. Skizze der Halswirbelsäule, teils in Normalstellung (ununterbrochene Linien), teils in der charakteristischen Fehlstellung. (Die Bewegungsmöglichkeiten nach H. Virchow, 1928, bestimmt).

topographischen Verhältnisse der Halswirbel und deren Bewegungen bei Beugungen der Halswirbelsäule in verschiedenen Richtungen, sind von H. Virchow (1928) sehr genau an Leichen untersucht worden, weshalb ich in dieser Hinsicht keine eigenen Studien gemacht habe, sondern mich auf die Beobachtungen dieses Forschers stütze. Es ist ebenfalls bewiesen worden, dass seine Feststellungen am toten Material mit den Verhältnissen an lebenden Individuen gut übereinstimmen. Zwischen den verschiedenen Wirbelkörpern liegen die elastischen Intervertebralscheiben, weshalb die Wirbeln — auf Grund der soeben beschriebenen Abschrägung

der oberen resp. unteren Flächen der Wirbelkörper kaudal von $C_3$ — geneigt sein müssen, sich im Verhältnis zum unterliegenden Wirbel ventralwärts zu verschieben. Dies hat zur Folge, dass die Lordose ausgerichtet wird. Die Wirbelsäule geht in einen geraden, kranial-ventral gerichteten Stab über oder es entsteht möglicherweise eine schwache Kyphose innerhalb dieser Partie. Kranial von $C_3$ resultiert eine entsprechende Steigerung der Lordose (s. Fig. 4). Hier sind indessen die statischen Verhältnisse besonders kompliziert. Ich gehe deshalb in diesem Zusammenhange auf die Belastungsverhältnisse im oberen und unteren Nackengelenk nicht näher ein, sondern verweise auf meine frühere Arbeit in der deutschen Zeitschrift für Chirurgie, Bd. 147, 1942.

Lässt man also die Funktion der Halsmuskulatur ausser Acht, würde bei einem vertikalen Druck der Halswirbelsäule diese eine Form annehmen, die mit derjenigen der oben erwähnten 16 Patienten übereinstimmen würde.

Die normale Belastung der Halswirbelsäule ist stets grösser als die eigene Schwere des Kopfes, da dessen Schwerpunkt bei Erwachsenen etwas oral von den Stützflächen für die Okzipitalkondylen liegt. Um zu verhindern, dass der Kopf nach vorn fällt, kontrahieren sich die Muskeln ständig, die dorsal von der frontalen Gelenkachse im oberen Nackengelenk befestigt sind. Diese Muskeln entspringen der Halswirbelsäule, dem Brustbein samt Schlüsselbein und verursachen einen gesteigerten Druck auf die Wirbelsäule.

Normalerweise verhindern die Halsmuskeln die beschriebene Formveränderung in der Halswirbelsäule, aber mit der Ausgleichung der Lordose im mittleren und unteren Teil der Halswirbelsäule werden Kopf und Hals ventralwärts verschoben. Dadurch erhält man einen grösseren Hebel zwischen der gemeinsamen Schwerlinie für den Kopf und Hals einerseits und der Befestigung der Halswirbelsäule an die Brustwirbelsäule andererseits. Die Muskulatur wird also dazu gezwungen, eine grössere Arbeit auszuführen als unter normalen Verhältnissen, damit die Halswirbelsäule und der Kopf nicht weiterhin ventralgebogen werden.

Man kann sich vorstellen, dass eine Formveränderung der Halswirbelsäule von oben geschildertem Aussehen in zweierlei Weise aufkommen kann:

1) Geschwächte Halsmuskulatur, aber normalschwerer Kopf.
2) Normale Halsmuskulatur, aber zu schwerer Kopf.

Um zu beweisen, dass die theoretischen, oben in Kürze skizzierten Gedankengänge richtig sind, welche durch Belastungsproben an einem einfachen Modell einer Halswirbelsäule samt an Leichen mittelst Röntgenkontrolle und mathematischdynamischer Berechnung bestätigt wurden, kamen folgende Versuche zur Ausführung. Als Versuchspersonen stellten sich 100 gesunde

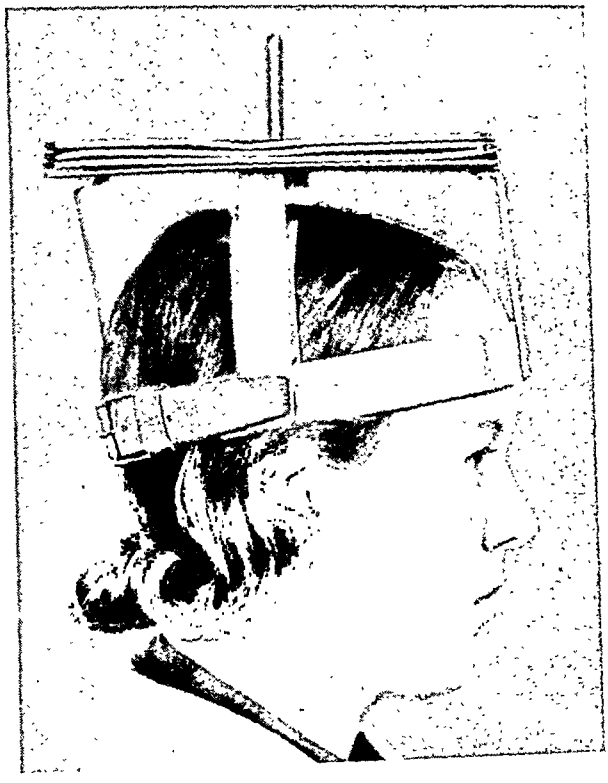


Fig. 5. Versuchsperson mit »Belastungskrone».

Studenten der Medizin (davon 25 weibliche) zur Verfügung. Für jeden wurde notiert:

1) Früher erlittene Krankheiten.

2) Früher während längerer Zeit ausgeführte körperliche Arbeit.

3) Sport, Art und Ausmass.

4) Konstitutionstypus.

Zuerst wurde mittelst Röntgendurchleuchtung in aufrechter Normalstellung die Form der Halswirbelsäule und deren Bewegungsvermögen in der Sagittalebene kontrolliert. (Röntgenaufnahmen erwiesen sich als unnötig, da sorgfältige Durchleuchtung

genügend war, um die Form und Bewegungen der Halswirbelsäule festzustellen). Alle Beobachtungen wurden während des Versuches einem Assistenten diktiert und sofort auf einer, für jede Versuchsperson in Ordnung gestellte Karte notiert. Darauf wurde der Kopf mit Bleiplatten von ca 12 kg Gewicht (s. Fig. 5) belastet. Die Schwerlinie dieser »Metallkrone» verlief durch



Fig. 6. Versuchsperson (H. R. ♂ 23 Jahre alt) mit Kopf und Hals in Normalstellung.

die Stützfläche des Schädels, d.h. derart, dass die Versuchsperson die Belastung auf dem Kopfe gleichmässig verteilt empfand und bei Normalstellung den Kopf weder vorwärts noch rückwärts oder seitwärts zu beugen wünschte. Die Versuchsperson musste in dieser Stellung während der ganzen Belastungsprobe, deren Zeitdauer vom Assistenten gemessen wurde, den Kopf stille und nach vorn gerichtet halten. Gleichzeitig wurde die Form der Halswirbelsäule mittelst Röntgendurchleuchtung beobachtet. Nach 1—4 Minuten, je nach der Muskelkraft der Versuchsperson, begann die Halswirbelsäule

bis drei Minuten, kürzere Zeit, wenn die Versuchsperson Kopf und Hals frei bewegen durfte und längere Zeit, wenn sie stille stand. Nachdem die Halswirbelsäule allmählich wieder eine vollkommen normale Haltung eingenommen hatte, wurde die Röntgendurchleuchtung an der Versuchsperson beendet.

Es ist zu bemerken, dass die beschriebenen Formveränderungen und Beschwerden ohne Ausnahme bei all den 100 Studenten und Studentinnen eintraten. Der einzige Unterschied war die Zeitdifferenz beim Aufkommen und Verschwinden der Veränderungen; Verhältnisse, die sich stets parallell zur Muskelkraft der betreffenden Versuchsperson verhielten.

Durch diese künstliche Belastung der Halswirbelsäule bei den Versuchspersonen erhielt man also eine Form derselben, die nebst den subjektiven Beschwerden praktisch genommen mit derjenigen vollkommen übereinstimmt, die wir früher bei den oben beschriebenen Patienten angetroffen haben.

Rein theoretisch gesehen müsste bei Belastung der Arme in Normalstellung, d.h. wenn der Schultergürtel einem indirekten Druck in kranio-kaudaler Richtung ausgesetzt wird, eine Formveränderung der Halswirbelsäule eintreten, die grösstenteils derjenigen entsprechen würde, welche bei starker Kopfbelastung resultiert. Dies beruht darauf, dass der Gürtel teilweise in Muskeln hängt, die dem Kopf und den beiden obersten Halswirbeln entspringen (M. trapezius, M. levator scapulae u.a.) und somit Druck auf die Halswirbelsäule ausüben — in gleicher Weise wie der Kopf. Ferner wird der Druck vom Schultergürtel auf den Brustkorb übertragen, wodurch dieser geneigt ist, einzusinken. Diesem entgegenwirken jedoch die Muskeln, welche von der Halswirbelsäule resp. vom Kopf ausgehen und sich an den oberen Rippen befestigen (Mm. scalen. ventr., med. et dors., die infra- und suprahyoidale Muskulatur, Mm. sternocleidomast. u.a.). Die Muskeln, die also von der Halswirbelsäule kommen und ventro-kaudal verlaufen, haben die Neigung, dieselbe vorzubeugen. Diejenigen dagegen, welche direkt oder indirekt vom Kopf kommen, tragen wie die erstgenannte Muskelgruppe dazu bei, den Druck auf die Halswirbelsäule zu vermehren.

Um zu beweisen, dass diese theoretische Erörterung reellen Grund hat, wurde einige Zeit nach der oben beschriebenen Belastungsprobe ein neuer Versuch mit denselben hundert Personen aus-

geführt. Zuerst kontrollierte ich mittelst Röngendurchleuchtung, dass die Form und Bewegungen der Halswirbelsäule normal waren. Dann bekam jede männliche Versuchsperson an jeder Hand eine Last von 20 kg zu tragen, bis sie ordentlich müde war. Der Student musste sich nun hinter den Durchleuchtungsschirm stellen, immer noch die Last tragend. Dasselbe wurde mit den weiblichen Ver-



Fig. 8. Dieselbe Versuchsperson wie in Fig. 6 u. 7 nach Armbelastung von 20 kg an jeder Hand während ca 4 Minuten.

suchspersonen vorgenommen, jedoch trugen diese nur 15 kg in jeder Hand. Die Durchleuchtung ergab, dass die Halswirbelsäule dieselbe Stellung einnahm, wie die erwähnten Patienten und Versuchspersonen bei der Kopfbelastung aufwiesen (s. Fig. 8). Diese Formveränderung der Halswirbelsäule blieb 1—4 Minuten bestehen, nachdem die Arme bereits wieder entlastet waren. Alle erklärten, dass sie ein starkes Müdigkeitsgefühl oder bohrenden Schmerz in den mittleren und unteren Teilen des Nackens verspürten. In keinem Falle kam eine Ausstrahlung der Schmerzen

nach dem Hinterkopf vor. Bei Palpation des Nackens fühlten die Versuchspersonen stets in der unteren Hälfte etwas Schmerz.

Es ist anzunehmen, dass die Deformierung der Wirbelsäule und das damit verbundene Müdigkeits-sowie Schmerzgefühl, wie wir es bei den Patienten angetroffen haben, auf zwei prinzipiell verschiedene Weisen entstehen kann:

1) Ein relativ zu schwerer Kopf.

2) Eine zu grosse Belastung des Schultergürtels.

Was ist die Ursache zur Deformierung in der Halsregion bei unseren zuvor geschilderten Patienten? Die theoretischen Möglichkeiten sind folgende:

1) Kongenitale Rückgratsdeformität von oben beschriebener Art. Eine solche hat, wie wir gesehen, eine bedeutend gesteigerte Tätigkeit der Halsmuskulatur zur Folge. Es ist denkbar, dass dies eine Muskelinsuffizienz trots normaler Muskulatur mit sich führt, was sekundär Kontrakturen mit Steifheit und Schmerzen veranlassen kann.

2) Eine gewohnheitsmässig erworbene falsche Haltung von Kopf und Hals, was ähnlich der gedachten, kongenitalen Deformität Muskelinsuffizienz mit begleitenden Beschwerden, trotz normaler Muskulatur, verursachen kann.

3) Minderwertige Muskulatur, die schon von Kindheit an die Halswirbelsäule nicht in Normalstellung zu halten vermag, sondern eine Insuffizienz mit oben beschriebenen Folgen bedingt.

4) Muskelzerstörung der einen oder anderen Art (Inaktivitätsatrophie, Myositen, primäre Myopathien u.a.).

5) Schwere Arbeit mit starker Belastung des Schultergürtels. Dies kann, wie ich experimentell gezeigt habe, zeitweilige Formveränderung der Halswirbelsäule herbeiführen. Bei wiederholter starker Belastung ohne genügende Hypertrophie der Halsmuskulatur kann man eventuell eine beständige Halsdeformität vermuten, die durch Überanstrengung der Muskulatur und Kontrakturzustand in derselben Schmerzen und Steifheit verursachen kann.

6) Erkrankung der Knochen oder Gelenke in der Halsregion. Diese Möglichkeit kommt allem Anschein nach nicht in Frage, da bei der klinischen und röntgenologischen Untersuchung der Patienten keinerlei Zeichen derartiger Krankheit festgestellt werden konnten.

Wahrscheinlich kann man annehmen, dass wir es hier entweder mit einer kongenitalen oder erworbenen Deformität der Halswirbelsäule zu tun haben. Sollte der Krankheitszustand erworben sein, dürfte man eine primäre oder durch Überanstrengung hervorgerufene sekundäre Muskelinsuffizienz vermuten. Gewohnheitsmässige Haltungsfehler sind weniger glaublich, denn kein Patient zeigte eine minder befriedigende Haltung. Die Beschwerden hatten



Fig. 9. Derselbe Patient wie in Fig. 1, 2 u. 3 nach Lokalnästhesie der Halsmuskulatur. Kopf und Hals sind maximal nach hinten geneigt.

sich bei allen erst als sie erwachsen waren eingestellt. Alle Fälle gehörten zu schwer arbeitenden Berufsgruppen, ausser zwei Frauen, die Schneiderinnen waren. Deren Tätigkeit muss wohl doch von diesem Standpunkt aus als ziemlich anstrengend gelten, da sie ja meistens mit dem Kopf in vorgebeugter Stellung arbeiten. Primäre Myopathien sind auszuschliessen, da keine anderen Merkmale solcher Krankheit wahrgenommen werden konnten. Auch dürfte man von Muskelrheumatismus absehen, da die klinische Untersuchung, wie oben erwähnt, keinen Anhalt hierfür gab.

Folgender Versuch, der an einem der weiblichen Patienten angewandt wurde, ist ein Beweis dafür, dass die Schmerzen von der Muskulatur ausgelöst werden. Wie aus den Figuren 1, 2 u. 3 hervorgeht, konnte Pat. die Halswirbelsäule, welche bei Ruhelage und Normalstellung in der charakteristischen Fehlstellung stand, nur sehr unbedeutend in der Sagittalebene bewegen. Pat. empfand im grösseren Teil des Nackens ein starkes Müdigkeitsgefühl und



Fig. 10. Derselbe Patient wie in Fig. 1, 2, 3 u. 9 nach neun Wochen langer Behandlung. Kopf und Hals sind maximal nach hinten geneigt.

bohrenden, zum Hinterkopf hinaufstrahlenden Schmerz. Bei Palpation zeigte Pat. leichte Schmerzhaftigkeit unten im Nacken. Die Muskulatur vom Nackenbein bis hinunter in Höhe von $C_7$ wurde mittelst 1 %-iger Novokainlösung anästhesiert. Pat. konnte darauf die Halswirbelsäule vollkommen normal bewegen (s. Fig. 9) und hatte während der nächsten 1 ½—2 Stunden keinerlei Beschwerden im Nacken.

Da man mit grösster Wahrscheinlichkeit annehmen kann, dass in den vorliegenden Fällen die Schmerzen und die Steifheit im Nacken von Überanstrengungen sowie Kontrakturen in der Nacken-

muskulatur herrühren, sollten derartige Zustände folgendermassen behandelt werden. Vor allem muss der Patient ordentlich ausruhen, damit die Kontrakturen weitmöglichst verschwinden. Danach wird lokale Wärmebehandlung verabfolgt sowie leichte Massage in möglichst schlaffer Haltung der Nackenregion (Pat. muss, auf einem Stuhl sitzend, den Kopf auf seine überkreuzten



Fig. 11. Derselbe Patient wie in Fig. 10 nach neun Wochen langer Behandlung. Kopf und Hals sind maximal nach vorn geneigt.

Arme stützen, die auf einem ca meterhohen Bock ruhen). Ferner werden aktive Bewegungen des Nackens ausgeführt. Pat. wird energisch ermahnt, beim Sitzen und Stehen den Kopf immer leicht nach hinten zu neigen, so dass in der Halswirbelsäule eine ordentliche Lordose zustande kommen kann. Die passendste Stellung wird mittelst Röntgendurchleuchtung ausprobiert und anfangs wenigstens einmal wöchentlich kontrolliert. Eine auf diese Weise durchgeführte Behandlung hat in den geschilderten Fällen zu gutem Resultat geführt (s. Fig. 10 u. 11), indem die meisten fast gänzlich frei von Beschwerden wurden.

## Zusammenfassung.

Verf. berichtet von 16 Patienten, welche von Müdigkeitsgefühl, Steifheit und Schmerzen im mittleren und unteren Teil des Nackens belästigt waren. Die Schmerzen erstreckten sich zuweilen bis zum Hinterkopf. Die Patienten zeigten leichte bis mässige Druckempfindlichkeit über der Muskulatur der beiderseitigen Spinalfortsätze in der Zervikalregion. Die röntgenologische Untersuchung in aufrechter Normalstellung liess in sämtlichen Fällen ein Verschwinden der Zervikallordose kaudal von $C_4$ und kranial davon eine Verstärkung derselben erkennen (Fig. 4.). Beim Versuch, die Wirbelsäule zu bewegen, geschah dies hauptsächlich kranial von $C_4$ (Fig. 1, 2 u. 3).

Verf. hält diese Krankheit für einen Insuffizienzzustand in der Muskulatur der Halswirbelsäule, auf primärer Rückgratsdeformität beruhend, was gesteigerte Tätigkeit für die Muskeln mit sich führt. Eine weitere denkbare Ursache kann Muskelschwäche (Asthenie, Inaktivitätsatrophie u. dgl.) oder starke Belastung des Schultergürtels ohne genügende Muskelhypertrophie im Halse sein.

Durch Insuffizienz und damit verbundene Deformität resultiert Überanstrengung sowie Kontrakturzustand in der Muskulatur, was Steifheit, Schmerz und Empfindlichkeit zur Folge hat.

Verf. zeigt an 100 gesunden Individuen zwischen 19 und 25 Jahren, dass entweder Kopfbelastung oder Belastung des Schultergürtels dieselbe Formveränderung des Zervikalrückgrates und die gleichen Beschwerden erzeugen kann, welche die Patienten aufwiesen (Fig. 6, 7, 8 u. 9).

Behandlung: Ruhe, um die Kontrakturen zu beseitigen, lokale Wärme, leichte Massage und aktive Bewegungen des Halses. Die Patienten wurden eifrig ermahnt, den Kopf stets etwas nach hinten gebeugt zu halten, um eine ordentliche Halslordose zu erhalten. Diese Stellung wurde mittelst Röntgendurchleuchtung kontrolliert. Die Behandlungsresultate waren immer von gutem Erfolg (Fig. 10 u. 11).

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# Feminizing Tumors of the Suprarenal Cortex, with Description of a Case.

By

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Tumors of the suprarenal cortex (adenoma, carcinoma) are often accompanied by changes in the sex characters in the form of abnormal masculinization. This so-called *adreno-genital syndrome*, which can be produced also by cortical hyperplasia, has recently met with considerable interest. The syndrome appears as different clinical types depending on the nature of the tumor and the point of time for its development (Table 1).

When the masculinizing effect commences in foetal life, a form of *pseudohermaphroditism* develops. The individuals have female gonads but male accessory sex characters. Pathologic-anatomically there is hyperplasia of the cortex, sometimes enlarged accessory suprarenals. In the *infantile form* the disturbance makes its appearance in the first years of life. In girls, who are attacked more frequently, the clitoris and labia undergo hypertrophy; in boys the penis is enlarged; both sexes have an increased growth of hair and a deep voice. Abnormally vigorous muscular development is seen, especially in boys. It seems uncertain whether this change in girls is always a clear-cut masculinization, as it has been claimed that growth of the breasts and appearance of the menstruation may occur in such cases. *Adrenal virilism* is observed in mature women, mani-

## Case Record.

Our patient, a farmer, 44 years old, was admitted to the hospital first on 9/3, 1940, and died on 4/6, 1941 during his fourth stay in the hospital (Reg. No. 477/1941).

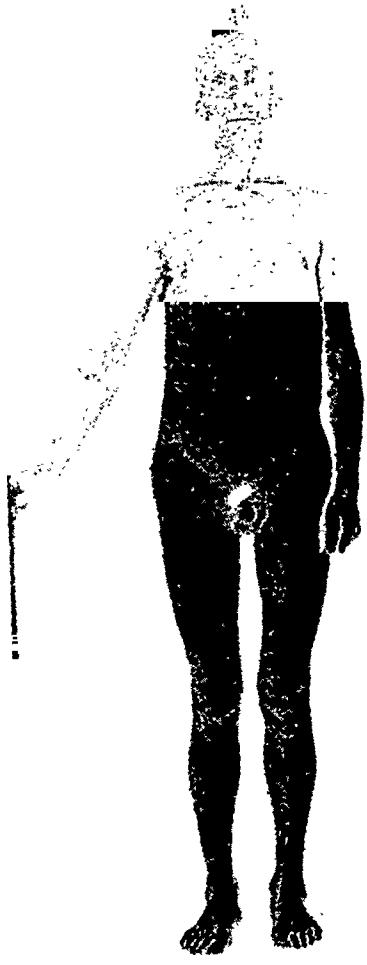


Fig. 1. Man, aged 44, with carcinoma of the left suprarenal cortex. Protrusion of the left hypochondrium. Gynecomasty.

***Family History.*** No disease of interest in the family.

***Past History.*** Mumps in childhood, possibly with bilateral orchitis. Rejected for military service on account of inguinal hernia on the right side, for which he was operated later. He has been married a number of years and led a normal sexual life. He has 4 healthy children, the youngest of whom is 3 ½ years old.

***Present Illness.*** For about 3 years both breasts have been increasing in size, sometimes tender. In the summer of 1939 tiredness and functional dyspnea began to appear, followed gradually by moderate loss of weight and oppressive pain localized to the anterior aspect of the left half of the chest. No distinct change in the hair or voice. Libido and potency are said not to have changed during his illness. He is unable to say whether the genitals possibly may have undergone any change.



Fig. 2. Close-up view of the gynecomasty.

***Physical Exam.*** Delicate of frame, thin, but with fairly well developed musculature. Height, 165 cm. Weight, 53.3 kg. Appearance healthy; ruddy complexion; strongly defined features. Virile type (Fig. 1).

*Mentality* normal; he is lively, bright, energetic, usually in a good temper.

Breasts both considerably enlarged (size of half an orange) and moderately tender (Fig. 2). Palpation reveals a considerable amount of firm, nodular tissue as a sort of corpus mammae. The nipples are large, the Montgomery glands conspicuous. No secretion can be expressed.

*Heart* and *Lungs* show no definite abnormality.

*Abdomen:* The left hypochondrium is slightly protruding. Under the left costal margin the palpation reveals a firm, nodular, indolent, non-movable *tumor*, the lower pole of which reaches 10 cm below the costal margin.

*Genitals:* Penis rather small. Right testis cherry-sized, left testis hardly walnut-sized. Left epididymis nodular and enlarged. The genitals are strikingly flaccid, the testes soft. On exploration the prostate feels normal in form and size.

*Hirsute* largely normal. Beard vigorous, pubes of virile type, somewhat scanty peripherally. A mere suggestion of hairiness on the anterior surface of the chest, scanty growth of hair on the extremities. No abnormal pigmentation, no acne.

***X-ray Exam.*** The *lungs* show numerous, large and small nodular tumor metastases in both lungs; also enlargement of the hilar lymph glands. In the upper part of the *abdomen*, on the left side, an intense shadow of soft parts is seen with an irregular area of calcification (size of a hen's egg) at the level of the 12th rib. The outline of the left kidney cannot be made out. After intravenous injection of hippoidin the pelvis of the left kidney is seen to lie at a low level, and it is twisted, so that the ureter sets off laterally, making in its course a laterally convex arc. No metastases seen in the bony system.

Thus the X-ray findings lend support to the preliminary clinical diagnosis: Malignant tumor of the left suprarenal with feminizing effect.

***Hormonal Analyses.*** Repeated analyses of the urine performed in the State Serum Institute (Dr. Chr. Hamburger) and in Løvens Kemiske Fabrik, showed a considerable increase in androgenic hormone and an enormous increase in estrogenic hormone, up to several thousand mouse units per day (Table 2). The values for gonadotropic hormone fell within the normal limits. The Friedman reaction was negative (March and October 1940).

***Other Examinations.*** *Urine:* No albumin, sugar, pus, blood, diacetic acid or acetone. No pathological elements on microscopy. $NH_3$ output in 24 hours: 0.88 g.

*Blood pressure* 135/85 mm Hg. *Sedimentation rate:* 35 mm/1 hour. Wassermann & Kahn negative. Mantoux positive (1 mg.).

*Hemoglobin* 105 %. Red blood count 5,100,000. Color index 0.93. White blood count 10,500. Differential count: Staff nuclear neutrophils 6.5 %, segment nucleus 62.5 %; eosinophils 0.5 %; lymphocytes 28 %; monocytes 2.5 %. Platelets 332,000. Coagulation time 2.5 min.

*Serum Cl* 380 mg %; serum Ca 9.9 mg %; Serum P 5 mg %. Total cholesterol 254 mg %; free cholesterol 80.5 mg %. Blood urea 24 mg %. Icterus index (Meulengracht) 5.

*Glucose tolerance test*, 70 g glucose: Blood sugar (fasting) 78 mg % → 195 mg % (45 min.) → 60 mg % (3 hours). No excretion of sugar with the urine.

**Table 2.**

*Hormone Content of 24-hour Urine in a Patient with Feminizing Suprarenal Cortical Tumor.* [1]

| Examiner ..... | L | S | S | L | L | S | L |
|---|---|---|---|---|---|---|---|
| Date ..... | 15—17/3 40 | 20/3 40 | 10/4 40 | 20—22/6 40 | 12—14/9 40 | 30/10 40 | 28—30/1 41 |
| Gonadotropic hormone (normal < 30 R.U.).. | < 30 | < 50 | < 50 | < 30 | < 30 | < 50 | < 30 |
| Androgenic hormone (normal 8—25 C.C.U.) | 54C. C.U. | ca. 350 I.U. | ca. 160 I.U. | 74 C.C.U. | 164 C.C.U. | 4—500 I.U. | 81 C.C.U. |
| Estrogenic hormone (normal < 20 M.U.).. | 2000 | ca. 5000 | > 4000 < 7000 | 1500 | 2500 | >2000 <8000 | 750 |

*Ewald test meal*, 45 min. 70 + 20 cm³, well chymified; free acid 70; total acidity 93.

*Electrocardiogram* normal. *Eye examination:* No abnormality.

**Course.** The condition of the patient was aggravated but slowly, with moderate loss of weight, tiredness, functional dyspnea and pain in the left side of the abdomen. Libido and potency decreased rapidly after his first hospitalization, and disappeared completely during the summer of 1940. Since then, no erection or pollution. Beard gradually getting softer, but no change in its rate of growth. No other change in the hairiness.

In July 1940 the patient had a brief attack of undoubtedly unspecific epididymitis on the left side. The breasts did not increase in size, but remained a little tender. The nipples, on the other hand, became gradually more prominent. There was no noticeable change in the penis, but the testes were undoubtedly decreasing in size, especially the left.

In January 1941 the tumor reached distally to the level of the iliac crest, medially to the midline. The margin of the liver was felt 4 cm below the costal margin. In the left supraclavicular fossa there was a bean-sized, hard lymph gland adhering to the underlying structures. True cachexia did not appear till late, together with cough, dyspnea, cyanosis and venous stasis of the left arm. The patient died in June 1941, 15 months after his first admission. Shortly before, his weight was 46.5 kg, sedimentation rate 102 mm, hemoglobin 78 % and red blood count 4,030,000.

***Autopsy*** (5/6—41). Marked emaciation (weight 43 kg). The growth of hair shows no definite deviation from the normal. No pigmentation of the skin. *Breasts* equally developed, measuring about 7 cm in diameter and

[1] The hormonal analyses were carried out by Lovens Kemiske Fabrik (L), after whom the normal values are cited, and by Dr. Chr. Hamburger, the State Serum Institute (S). *N. B.!* The values for androgenic hormone are given partly as cock's comb units, partly as international units.

2.5—3 cm in thickness. Nipples somewhat prominent, measuring 7 mm in diameter. *Thyroid* not enlarged, measuring 4 cm in height, lateral lobes 1.5 cm in width and 2 cm anteroposteriorly; no cysts or tumors. Notwithstanding thorough search, it is not possible to demonstrate any *thymus*. *Parathyroids* not visible. *Trachea* containing abundant, thick, yellowish pus. On both sides of the trachea, some nodular lymph gland metastases, up to 3 cm in diameter; cut surface whitish, markedly necrotic.

*Pleurae:* No accumulation of fluid; numerous fibrous, partly cord-like, adhesions on both sides. The surface of both *lungs* is studded with large, round, projecting, nodular metastases, distributed equally on the two sides. Most of these nodules measure 2—4 cm in diameter and are dark-greyish in color. Also the cut surface of the lungs is studded with almost spherical nodes, some of which show a slightly lobular pattern and central yellowish necrosis. The nodules stand out prominently and are quite sharply defined against the surrounding lung tissue so that they can be enucleated. The surrounding lung tissue shows oedema, stasis and scattered areas of bronchopneumonia. The peribronchial and hilar lymph glands show metastases.

*Pericardium:* No accumulation of fluid or tumors.

*Heart*, measuring 8 × 9 cm and weighing 220 g is atrophic, with gelatinous atrophy of the subpericardial fat tissue and marked brownish coloration of the myocardium. The right and left ventricles measure respectively 12 mm and 4—5 mm in thickness. Valves and ostea normal. No fibrosis or myomalacia; no metastases. *Coronary arteries* very tortuous, without arteriosclerotic changes. *Pulmonary artery* shows no emboli, no sclerosis. Aorta shows merely a very slight degree of arteriosclerosis.

*Oesophagus:* No abnormality.

No ascitic fluid in the *peritoneal cavity*. In the left hypochondrium a large retroperitoneal tumor is protruding, extending down to the rim of the pelvis.

*Stomach:* No tumor or ulcer. On the outside of the fundus, a couple of hazel-nut-sized lymph glands with metastases are firmly adherent to the stomach wall. Small intestine, colon and rectum normal.

*Liver*, somewhat enlarged measuring 30 × 22 × 7 cm. Weight 2250 g. Surface dark, brownish, with 5 protruding metastases, up to 4.5 cm in diameter, with pronounced umbo formation. The intermediate tissue shows a normal, not granular, surface. The cut surface presents 6—7 metastases, from 0.5—3.5 cm in diameter, without pronounced necrosis; like the metastases in the lungs, they are well-defined against the parenchyma, which is dark-brown in color, with normal configuration.

*Pancreas* and *spleen* normal in size, form and consistency. The *lumbar lymph glands* are the site of large, nodular metastases.

*Right suprarenal*, 3 × 4 × 4 cm. Beneath the cortex, at the lower pole, corresponding to a thickening of the surface, is a well-defined area of uniform yellowish tissue, which is removed for microscopy.

*Left suprarenal:* This organ is replaced by a large, roundish, irregular, nodose retroperitoneal tumor measuring 25 cm in length, 16 cm in width and 15 cm in thickness, and weighing 2650 g (Fig. 3). The descending colon

is located laterally and posteriorly to the tumor and the spleen. The cut surface of the tumor presents a very motley picture with varying, greyish-red, markedly necrotic areas, hemorrhages here and there, and yellowish, firmer areas with patches of necrosis, surrounded by rather coarse, fibrous, connective tissue septa.

*Kidneys* of normal size, 11 × 5.5 × 2.5 cm. The left kidney is slightly dislocated; no kinking of the ureter. The surface of the kidneys is smooth;



Fig. 3. Tumor arising from the left suprarenal cortex (weight 2650 g).

cut surface dark, reddish, with normal configuration; no metastases or ingrowth of the tumor. Pelvis and ureter not dilated; no sign of infection of the urinary passages.

*Testes* small and atrophic. The right measures 2.5 × 1.3 × 1.2 cm, and weighs 10 g. The left measures 3 × 1.5 × 1 cm, and weighs 14 g. No sign of tumor development.

*Prostate* and *seminal vesicles* apparently normal. Prostate measures 1.3 × 2.2 × 3.4 cm., and shows no sign of tumor development.

*Brain:* The basal arteries and meninges appear normal. On section the brain shows no hemorrhage, softening or tumor formation. *Hypophysis* normal in form and size, weighing 0.6 g.



Fig. 4. Suprarenal cortical tumor with perithelial arrangement of the cells (in rosettes). Van Gieson-Hansen. Magnif. × 100.

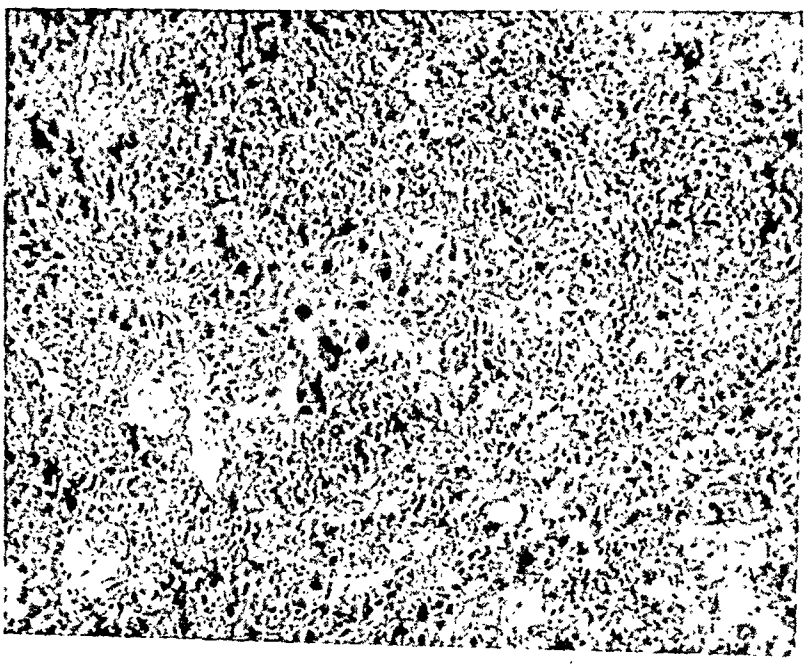


Fig. 5. Another part of the tumor with cellular *polymorphia*. In the center groups of large cells with hyperchromatic nuclei. Van Gieson-Hansen. Magnif. × 100.

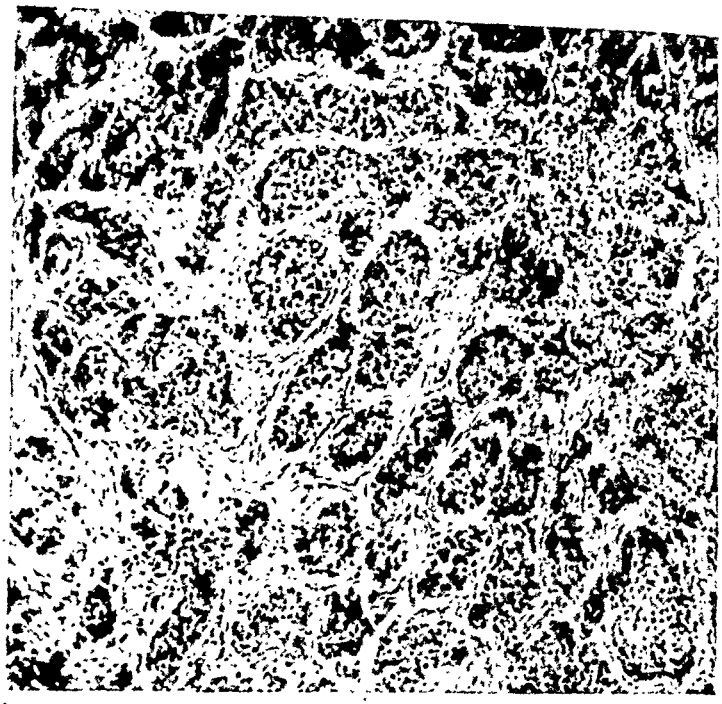


Fig. 6. Metastasis in the liver; alveolar grouping of the cells. Van Gieson-Hansen. Magnif. × 100.

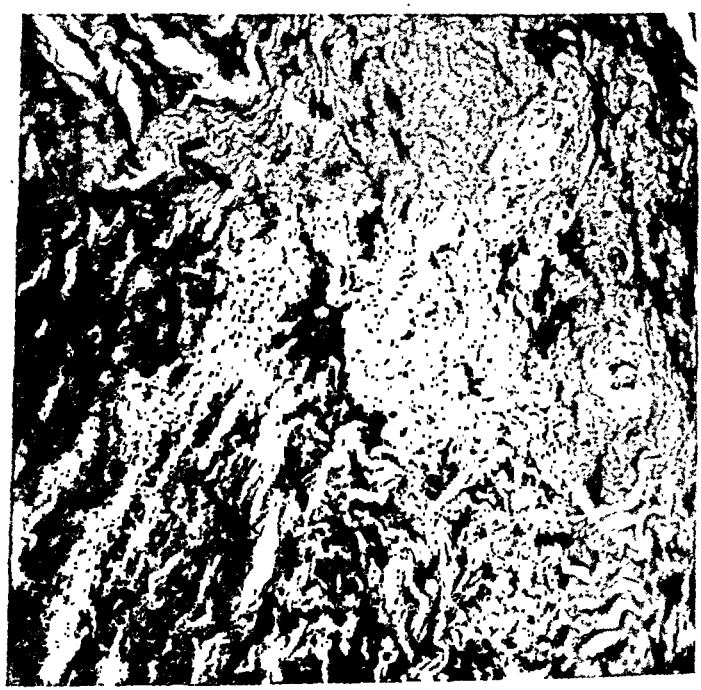


Fig. 7. Pronounced fibrosis of the breast with a few glandular ducts. Van Gieson-Hansen. Magnif. × 100.

***Epicrisis.*** In a previously healthy man, aged 44, gynecomasty develops in a couple of years. On admission to the hospital the breasts have reached the size of half an orange and are moderately tender. Both testes are atrophic and soft. A tumor is ascertained



Fig. 8. Atrophic testis with markedly hyalinized tubules and fibrosis of the interstitial tissue. Van Gieson-Hansen. Magnif. × 240.

in the upper left part of the abdomen, evidently arising from the left suprarenal, besides numerous metastases in both lungs. Examination of the urine reveals a considerable increase in androgenic hormone and a very great increase in estrogenic hormone, up to several thousand mouse units per day. During the further course of the illness libido and sexual potency disappear completely. The patient dies 15 months after his first hospitalization, with late cachexia.

The autopsy reveals a large tumor (weighing 2650 g) arising from the left suprarenal, and metastases in the liver, lungs, numerous lymph glands and right suprarenal, the cortex of which is hyperplastic. Microscopy of the tumor and metastases shows a cortical carcinoma, made up of polymorphous epithelial cells, the arrangement of which in several places reminds of suprarenal cortical tissue. The breasts consist of fibrous tissue surrounding scattered, glandular lumina. The testes are markedly atrophic with hyalinization of the tubules, together with fibrosis and atrophy of the interstitial tissue. The anterior lobe of the hypophysis shows fibrosis of the interalveolar septa, but no definite change in the proportion between the various types of cells.

## Cases Described Previously.

Since 1919 descriptions have been given of altogether 6 more or less thoroughly examined cases of feminizing cortical carcinoma in mature men, namely by Bittorf (1919), Mathias (1922), Parkes Weber (1926), zum Busch (1927), Holl (1930), Lisser (1936) and Levy Simpson & Joll (1938).

The case described by Bittorf, and examined post mortem by Mathias, was that of a man, 26 years old who from August 1918 had an increasing enlargement of the breasts, followed in the beginning of 1919 by atrophy of the testes and decrease in sexual potency. On examination in April 1919 his breasts were found to be of female type, the testes were soft and hardly as large as peas, and a large tumor was felt in the left side of the abdomen. The hairiness was normal, of virile type. There were spots of pigmentation on the margin of the eyelids and perhaps a slight pigmentation of the face. Cachexia developed slowly. Autopsy revealed a tumor arising from the suprarenal cortex and metastases in the liver. On microscopic examination the tumor showed short, glandular loops of irregular structure. The breasts consisted of loose, fibrous tissue with a few, slightly ramified, glands. The testes showed spermatogenesis, but the interstitial cells were hardly recognizable.

The patient reported by Parkes Weber was a man, aged 27, in whom an indolent enlargement of the breasts was observed from September 1915. A few drops of slightly milky fluid could be expressed from the nipple. The patient died in December 1915.

**Table 3.**

*Schematic Survey of the Symptoms in the Reported 7 Cases of Feminizing Carcinoma of the Suprarenal Cortex.*

| Author | Year | Age on admission | Gynecomasty | Secretion from breasts | Atrophy of testes | Reduction or cessation of libido and potency | Obesity | Decreased growth of hair | Pigmentation | Acne | Abnormal excretion of hormones |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bittorf | 1919 | 26 | + | | + | + | 0 | 0 | (+) | | |
| Parkes Weber | 1926 | 27 | + | + | | | | | | | |
| Holl I | 1930 | 15 | + | | 0 | | | (+) | (+) | | |
| Holl II | 1930 | 44 | + | | + | + | + | (+) | 0 | + | |
| Lisser | 1936 | 33 | + | + | | | | 0 | | | |
| Levy Simpson & Joll | 1938 | 34 | + | | + | + | | (+) | | | + |
| Roholm & Teilum | 1942 | 44 | + | 0 | + | + | 0 | (+) | 0 | 0 | + |

Autopsy (zum Busch) showed a malignant tumor arising from the cortex of the left suprarenal, with metastases to the lungs, pleurae, mesenteric and cervical lymph glands. The breasts were of the female type and secreting.

Holl has observed two cases. One was that of a boy, aged 15, in whom a tumor in the right hypochondrium was noticed two months before hospitalization. His facial features were soft and there was no growth of beard at all. Both breasts were somewhat enlarged, with pigmented areolar. The abdomen showed a linea fusca from the umbilicus to the symphysis, as in pregnant women. The genitals were normal, the pubes of feminine type. Operation disclosed an inoperable tumor, size of a man's head, arising from the right suprarenal. The patient died six months later, with terminal cachexia. Autopsy was not performed.

The second case of Holl is unique. A man, aged 44, previously healthy and the father of two children, presented the following symptoms from autumn 1927: The breasts became tender and commenced growing, to the size of an apple, and the areolar became pigmented. The penis and testes decreased in size, libido disappeared, and there was no erection or pollution. The patient became fat, and an acne appeared; the previously virile facial fea-

tures were softened. The hairiness became more scanty, but its male type was preserved. On operation in July 1929 a tumor (size of two fists) arising from the left suprarenal was removed. Microscopy showed the tumor to be rich in cells that were markedly polymorphous; the structure of the tumor reminded of the zona fascicularis. Within a few days after the operation the acne disappeared, the breasts decreased in size and were no longer tender. From autumn 1929 the patient's sexual life was normal. His facial expression was changed, becoming more virile again, the adipose tissue diminished and the external genitals increased in size and became more firm.

Lisser's patient was a man, 33 years old, who for one month had noticed a loss of weight and pain in the left flank. The breasts were noticeably enlarged, firm but not tender, and sometimes a watery fluid could be expressed from the nipple. His appearance and hirsute were masculine. Unfortunately, the report says nothing about the genitals. Autopsy revealed a large tumor (weighing 625 g) arising from an accessory suprarenal on the left side, and metastases in the lungs. The tumor was made up of small cells arranged in a pseudoadenomatous manner. Some cells were large and contained several nuclei.

The case most thoroughly examined was reported by Levy Simpson & Joll, observed in a previously healthy man, 34 years old and the father of one child. In 1932 he noticed an enlargement of the breasts; in August 1933 the libido was lost and the potency greatly decreased; the genitals diminished. In July 1934 a malignant adenoma (weighing 656 g) arising from the left suprarenal was removed. On microscopy the tumor showed cells in perithelial arrangement and occasional differentiation into three zones, reminding of the normal suprarenal. Hormonal analysis on the day after the operation showed > 500 M. U. of estrine per liter of urine. During autumn 1934 the patient gained in weight, the size of the breasts decreased, the genitals became larger, and the libido and potency returned again to some extent. At this point of time the urine contained less estrogenic and androgenic hormones than normally. From spring 1935 the breasts again increased in size, and the patient became impotent. Laparotomy in April 1936 revealed metastases in the liver; and the patient died in June 1936. Hormonal analyses in November 1935 and January 1936 showed >

3000 M. U. of estrine per liter of urine and a slight increase in androgenic hormone ($> 50 < 100$ cock's comb units). The Aschheim-Zondeks reaction was negative in June 1935, and January 1936. Analysis of the morning urine voided on the day of the operation (July 1934) showed no gonadotropic hormone (Burrows and collaborators).

## Discussion.

The symptoms in the 7 published cases of feminizing cortical carcinoma of the suprarenal are recorded schematically in Table 3. In several of these cases the data are incomplete. Thus information about the condition and function of the genitals is wanting in the cases reported by Parkes Weber and by Lisser. In all 7 cases the tumor was examined either on autopsy or operation, and its relation to the suprarenal was established. Previously microscopy of the breasts was performed only twice (Bittorf, Parkes Weber), of the testes only once (Bittorf). A thorough autopsy has been reported only in our case.

Notwithstanding the incomplete data it is obvious that cortical carcinoma in mature men in rare cases is accompanied by symptoms from the genital system, namely: gynecomasty, genital atrophy and loss of the sexual function. These phenomena were present in 4 of the best examined cases. Holl states that in one of his patients (the 15-years-old boy) the genitals were normal, it is true, but this fact as well as the slight gynecomasty are probably explained by the unusually rapid course of the disease, only a few months passing between the recognition of the tumor and exitus. Moreover, an important symptom, demonstrated in the two last described cases, is a very considerable increase in the estrogenic hormone content of the urine together with a more moderate increase in the amount of androgenic substances. In their patient Levy Simpson & Joll found a maximum of $>$ 3000 M. U. of estrine and 50—100 C. C. U. of andrine per liter of urine. Our patient excreted up to about 5000 M. U. of estrine and 50—80 C. C. U. of andrine per 24 hours.

On histological examination the breasts show fibrosis with some lumina of mammary glands here and there. In our case the testes were quite atrophic, with loss of tubular epithelium as well as interstitial tissue. The hypophysis showed some fibrosis but no change in the proportion between the normal cell forms.

The other symptoms are not particularly conspicuous. Generally there is no change in the virile type of the body. A slight reduction in the hairiness has been described in some cases, it is true, but apparently an increase in the subcutaneous adipose tissue occurred only in one of the cases described by Holl. No change in voice has been reported. No sexual perversion appears to have been noticed. Slight pigmentation may occur, but as a rule there is no sign whatever of cortical insufficiency as seen sometimes in association with cortical tumors. None of the cases here mentioned was examined with a view to the cortical hyperfunction that has been described in a few cases of virilizing tumors resulting in a change in the quantitative proportion of plasma electrolytes opposite to the change characteristic of Addisson's disease (McQuarrie and collaborators) or increased excretion of cortical hormone with the urine (Westman).

In 6 out of the 7 cases described the tumor arose from the left suprarenal. Metastasis took place most often to the liver, lungs and lymph glands. In our case tumor tissue was found also in the opposite suprarenal, a not uncommon phenomenon in malignant cortical tumors. In some case the course of the disease was rapid, in others more protracted, with an interval of several years between the onset of the clinical symptoms and exitus. Probably metastasis takes place as a rule rather early. Holl was able to remove a tumor radically after it had given symptoms for nearly two years, it is true, but the malignancy of this tumor seems questionable. On an average the size of the tumor was considerable; the cortical carcinoma in our case appears to have been one of the largest recorded so far (2650 g).

Macroscopically the feminizing carcinomata look like other cortical carcinomata, being yellowish in color, soft, deteriorating, with tendency to hemorrhage and necrosis, solid or with cystic cavities from deterioration.

Histologically distinction has been made between different forms of cortical carcinoma. *Adenocarcinoma* (or malignant adenoma) shows here and there some atypical areas, but the arrangement of the cells is often similar to that seen in normal suprarenal cortex, especially zona glomerulosa and fasciculata. The cells resemble the normal cortical cells but are large, with hyperchromatic nuclei. Lumen formation is a rare finding. There is no diffuse growth as in the *fully developed carcinoma.* Here the cells are large,

granular, often with perivascular arrangement. Sometimes numerous giant-cells are seen in the tumor and the metastases. Such tumors have been described as sarcomata or carcinosarcomata, presenting both areas of carcinomatous type with perivascular or alveolar arrangement and also compact streaks of spindle-shaped cells. In the completely diffuse forms the cells have lost all resemblance to normal cortical cells.

In the present case the tumor shows a sort of transition between the two first-mentioned forms: Only in a few areas does it present a picture corresponding to the more differentiated malignant adenoma observed in Levy Simpson & Joll's case. A histological distinction between feminizing and virilizing cortical tumors of the suprarenals has been attempted by Ross (cited after Levy Simpson & Joll), but it is hardly practicable. In our case it will be reasonable to emphasize the striking resemblance between the histological picture of the tumor (see Fig. 5) and the cortical carcinoma depicted by Goldzieher from a case of pubertas precox (The Adrenals, 1929, Fig. 66), while the morphological resemblance to Levy Simpson & Joll's of feminizing tumor is far less pronounced.

In 34 out of 36 examined cases of virilism, Broster & Vines found cortical cells staining red with Ponceau fuchsin, and they assume that the fuchsinophilic substance — which, as a matter of fact, occurs in either sex during the first half of fetal life — contains a masculine hormone. Grollman, on the other hand, prefers this hormone formation to the so-called androgenic zone or x-zone situated between the cortex and the marrow, and claims that an increase in this produces the adrenogenital syndrome. So far, no definite relation has been demonstrated between the androgenic zone and the fuchsinophilic zone, and the question as to which cortical cells are the site of the abnormal hormone production has not yet been settled.

As mentioned in the introduction, the adrenogenital syndrome may be observed also in persons who are not suffering from cancer or adenoma but present a hyperplasia of the suprarenal cortex. Possibly feminization in men may take place on the basis of cortical hyperplasia. Glass & Bergman have reported cases of subclinical adrenogenital syndrome in men with gynecomasty, testicular atrophy and relative increase in the estrin output of the urine. Probably, such a clinical picture may develop also in the absence of a suprarenal lesion.

The presence of gynecomasty and testicular atrophy are criteria to the value of diagnosis of the feminizing cortical tumor of the suprarenal. The decisive criterion, however, is the demonstration of the tumor itself. The hormonal analysis may be of great importance in differential diagnostic respect too — for instance to differentiate the lesion from the rare forms of chorionepithelioma of extragenital localization. Heiberg & Hamburger have described an interesting case of this kind. A man, aged 38, presented a tumor in the left kidney region and gynecomasty. The urine contained 800—1000 mouse units of estrin per day, and hence the possibility of a suprarenal tumor was considered. Hormonal analysis of the urine showed also a great gonadotropin content, however, — one million I. U. per liter of urine — and this is characteristic of chorionepithelioma. Autopsy confirmed this diagnosis; no tumor tissue was demonstrated in the testes. In cases of cortical tumors the gonadotropin content of the urine is not increased. This applied also to Levy Simpson & Joll's case and to our own case.

The changes in the sex characters observed in patients with cortical tumors might be explained as attributable to a disturbance in the normal balance between the sex hormones of the organism produced by the tumor. Many women with virilism have shown a great amount of androgenic substances in the urine (Bühler, Bruins Slot, Levy Simpson and collaborators, and others). In contrast hereto, in two cases of feminizing cortical tumors in men (Levy Simpson & Joll, and the present case) the urine contained a large amount of estrin-like subtances. The matter is not as simple as that, however. In cases of virilizing cortical tumors the excretion of androgenic substances may fall within the normal limit (Westman), and the estrin content of the urine may be greatly increased (Frank, Cahill and collaborators, Dingemanse & Laquer and others). These apparently paradoxical findings may be explained as owing to the circumstance that the male and female sex hormones chemically are closely related compounds which may easily be altered. Differences in the technique of the hormonal assay give highly different results (Lukens and Palmer).

Male urine may normally contain estrin in varying amounts, as a rule less than female, and it has been possible to isolate and identify the estrin in male urine (Laqueur and collaborators). Also in castrates, male as well as female, the excretion of estrogenic

substances with the urine can be illustrated by means of the Allen-Doisy test, although in smaller amount than in normal individuals (Hart Hansen). The view has been advanced that these substances originated from the suprarenal cortex (Parkes). Several substances with a pronounced andrin effect have been demonstrated in the cortex (Reichstein). According to Verzár the suprarenal cortex produces the fundamental substance of the sex hormones, which is derived from cholesterol, while the transformation to specific sex hormones takes place in the gonads. While this transformation of cholesterol derivatives, equipped more or less with properties of sex hormones, does not cease completely on castration (Hart Hansen), *under pathological conditions an increased or abnormal cellular activity may give rise not only to an increased production of normal sex hormone, but also to the formation of other steroid substances able to influence the accessory sex characters.* Presumably the virilizing and feminizing effect of cortical tumors is to be explained in this way.

Like the suprarenal cortical hormone corticosteron, which is a derivative of the corpus luteum hormone progesteron, the specific sex hormones are derivatives of cholesterol. Decomposition of cholesterol (over dehydroandrosterin as an intermediate stage), by hydration or dehydration, results in compounds of androsterin type or estrin type, respectively. These facts also explain the synchronous occurrence of different types of hormone (Butenandt), as similar processes are assumed to take place in the living organism, normally in the gonads.

Indeed, the effect of the removal of the tumor indicates that the abnormal hormone production has to be ascribed to the abnormal suprarenal cortex. In Holl's patient the feminine features began to subside very soon after the operation. In Levy Simpson & Joll's case the amount of estrogenic substances in the urine fell off from more than 500 M. U. per liter to subnormal values; and later, when metastases developed, the value increased again to more than 3000 M. U. per liter. Corresponding observations have been made in women with virilizing tumors.

A few studies have been reported on the hormonal content of virilizing cortical tumors. Friedgood & Gargill demonstrated the presence of androgen, whereas Kenyon and collaborators failed to find this substance. In Bruins Slot's case the hormonal content of the tumor was not greater than that of other tumors, although

this woman excreted 2000 C. C. U. of andrin and 1000 M.U. of estrin per liter of urine. Westman found only 6 C. C. U. of andrin in the entire tumor, although the woman excreted at least 20,000 C. C. U. of andrin per liter of urine. The negative outcome of such analyses does not necessarily mean that the active substances are not formed in the tumor. Indeed, the hormonal content of active secretory glands may be only slight.

The mechanism in the feminizing (or virilizing) process hinges on a hormonal influence on the heterosexual sex characters present in the organism in a latent form. Transformation of sex is easily producible in castrated animals (Steinach, Sand). In non-castrated animals, too, it is practicable, albeit more difficult, to alter the sex characters. Thus, administration of estrogen substances to male animals produces in variable degree a growth of the mammae glands and atrophy of the testes and penis (*e. g.*, Frazier & Mu; Nelson), that is changes corresponding to findings in the adrenogenital syndrome in mature men.

In our case the thymus could not be demonstrated. Normally this gland subsides in size after puberty, and hence the abnormal production of sexual hormones may be assumed to have brought about a complete disappearance of this gland. The prostate was normal, macroscopically as well as microscopically, and this is interesting in view of the theory advanced recently, that hypertrophy of the prostate depends on disturbances in the production of sex hormones. Experimentally it is practicable in animals to produce hypertrophy of the prostate by injection of estrogenic hormones.

## Summary.

A previous healthy man, aged 44, with a cortical carcinoma arising from the left suprarenal, presented gynecomasty, diminution of the testes and increased excretion of androgenic and, especially, estrogenic substances in the urine (up to several thousand mouse units per day). During the course of this lesion the libido and potency disappeared completely. Autopsy revealed pronounced atrophy of the testes. The breasts consisted of fibrous tissue with scattered glandular lumina here and there. The anterior pituitary was the site of some fibrosis, but there was no change in the normal proportion between the different types of cells.

The adrenogenital syndrome in men is discussed and the six cases described previously of feminizing cortical tumors in men are cited in detail. Now the existence of such tumors has to be considered established. The abnormal hormone production is attributed to the pathologically altered suprarenal cortex which is assumed not only to be able to produce normal sex hormones but also other steroid substances capable of influencing the accessory sex characters.

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# The 24-hours' rhythm in diabetes.

By

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In raising the question of the 24-hours' rhythm in the function of the organs, in connection with diabetes, I will not undertake to add new clinical data to those already existing. The object of this study is to investigate whether the rhythm manifests itself in diabetes, and if so, whether it would prove to be of any importance to explain various clinical facts, and to alter our conception regarding the treatment.

Forsgren and his collaborators have proved that a 24-hours' rhythm does exist in the function of animal organs, (1, 7, 8, 9, 10, 11, 24, 25, 26, 27) and they have laid the basis for the hypothesis, that a similar rhythm is found in the human organism.

Since this important quality of the function of human organs is not manifest, a special method is necessary to demonstrate it. Hence I have spent several years on the development of a suitable technique, in the course of which I arrived at the conclusion, that it is possible to obtain a clear and equable rhythm in the excretion of urine, if the following conditions are observed:

1. the hourly supply of liquid may not exceed 30 cm (16) Even in case of thirst a decidedly rhythmical excretion can be seen.

2. the supply of food must be regular: either no food at all, or distributed in equal hourly portions over a period of 24 hours.

3. the test person may not change from a standing to a lying posture. (18) This means, that he must remain in bed all the time.

If, under these circumstances, the urine is measured hourly and its respective constituants are determined, the excretion will be found to be rhythmical. (13, 14, 15) showing a minimum after midnight and a maximum at 2 p. m. former Amsterdam time, whilst the maximum will repeat itself as many times as the experiment lasts 24 hours. (17) This also applies to healthy persons individually. After elaborate investigation I have found, that the formation of urea by the liver has a rhythmic course. (19)

My opinion that, in spite of the criticism by Higgins (22, 23) and Deuel (6) on the data of the animal experiments, all human organic functions show a 24- hours' rhythm is, however, not only based on the results of my own experiments, which proved this with regard to the liver and kidney functions, but also on the fact, that any argument in favour of the functional constancy during 24 hours, is lacking.

Finding a perfectly constant concentration of sugar and urea in the blood of healthy persons, examined by this method, I fully endorse, as far as the blood is concerned, what Claude Bernard was the first to formulate: »La fixité du milieu intérieur est la condition de la vie libre, indépendante.» (3) The same conception was expressed by Cannon, (5) in another word — homeostasis.

If the blood is constant and the function of the organs rhythmical, the problem of the composition of the interstitial fluid becomes acute. With regard to this problem Claude Bernard expresses himself as follows: »Il est ainsi, parce qu'en réalité, le milieu intérieur, qui enveloppe les organes, les tissus, es éléments des tissus, ne change pas.» (2) *It* seems to me, however, that our technique has not advanced far enough yet, to justify such a conclusion.[1]

Armed with this method and guided by these reflections, which apply to healthy people, I examined whether these conceptions would also apply to diabetic patients.

I first ascertained, by examining 6 diabetic patients, that the excretion of sugar, on a constant supply of 30 cm of water, and the

[1] Peters, J. P. »Body Water», London, 1935, p. 36: »By direct analysis nothing is known of the chemical composition of normal interstitial fluid, because, under ordinary circumstances, it does not appear in large enough deposits in any part of the body, to permit sampling.»

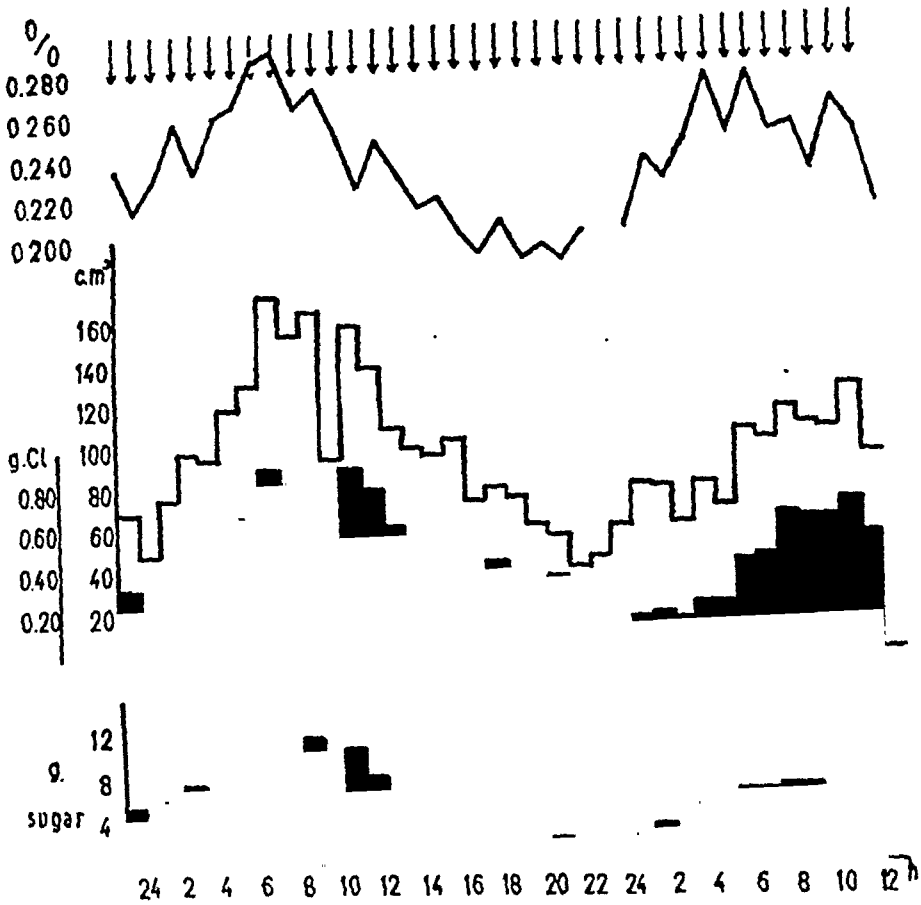
same amount of carbohydrate per hour, has a rhythmic course. The maximum, which, owing to the introduction of central European time in this country, I had expected at 4 p. m. was indeed found at 10 a. m. It is possible, that the change, which diabetes causes in the organism as a rhythmic system, is followed by the deplacement of the maximum, which deplacement is very common in relaxation oscillations. (4.38). I regret to be unable to give a further explanation.

The amplitude of the rhythmic excretion of sugar in these 6 diabetic patients was such, that on an average, during the hours of the maximum, 3 times as much sugar was excreted as during the minimum, thus showing the significance of these oscillations, which are caused endogenously.

After these preliminary experiments, I have made a complete experiment on a young diabetic, which test I since repeated on several others. They lead, in principle, to the same result. Therefore I consider the diagram, published here, as characteristic for diabetic conditions.

Every hour 30 cm of water and the same amount of food (consisting of 5 g of carbohydrate, 2.7 g of protein and 3.5 g of fat) was given to the testperson. Every hour his bloodsugar was determined (Hagedorn-Jensen) and in addition the diuresis and the amount of excreted chlorides (Volhard) and sugar (polarimetric). This was done for a period of 40 hours, so as to be able to show the repetition of the maximum as well. Brief experiments, covering only one phase or a fractional part of the rhythm, cannot be considered as sufficient. (20)

The bloodsugar is clearly rhythmical, in contrast with the bloodsugar in healthy persons, which, under the same experimental conditions, is constant. That a substance is present in the blood in a constant concentration, supposes that the supply to, and the disappearance from the blood, happens at the same rate, i. e. that the functions concerned are synchronised and that the amplitude of their rhythm is of the same magnitude. This must be the case as regards the bloodsugar in healthy persons. In diabetes the supply of glucose to the blood is no longer compensated by combustion or storage, resp. excretion. That is why changes in the bloodsugar result, which, under these conditions, are rhythmic.




Bloodsugar and excretion of water, chlorides and sugar in diabetes.

In the literature I found the following about the changes of the bloodsugar during 24 hours (12): in the morning, either before or after breakfast, high; after that declining, till the lowest point is reached in the afternoon; then, during the evening and night, a rise, which is especially pronounced early in the morning, until a high fasting value is attained. (29, 30, 36, 37.) From this it appears, that this course of the bloodsugar during the 24 hours, is well known, only the explanation is different. The »paradoxical rise» of Hatlehol (21) is no longer contradictory, but fits in perfectly with the conception of the 24-hours' rhythm. The opinion expressed by Hatlehol himself, as well as the view held by Peters and van Slyke, which hold sleep and the formation of sugar from protein respectively responsible for the nocturnal increase, may be rejected as being insufficiently founded.

For lack of a method with which the rhythm in the diuresis

can be pursued, it has hitherto been unknown that the sugar excretion has a rhythmic course. I found the maximum excretion of sugar in this case 8 times as high as the minimum. Here too, the well-known parallelism between bloodsugar and glucosuria is found to exist.

The practical interest of these considerations might be shortly summarised as follows: when judging glucosuria and bloodsugar it is necessary to consider the time of the day, to which the data are related. The indication »fasting» is of less importance than the knowledge that the quantity of these substances is increasing or decreasing.

The 24-hours' rhythm is of great interest for the treatment. It is unjustifiable to allow an exogene charge with carbohydrates to take place in a period, when the organism produces an abundance of sugar, and a high bloodsugar is present, whilst, at the same time, the excretion of sugar has reached its maximum. On the other hand the diabetic patient may be allowed more freedom during the time, when the secretion of sugar is minimal and the bloodsugar is low, hence, in the assimilative period. Thus, it becomes more important When the diabetic patient eats, than What he eats.

Although Möllerström (31, 32, 33, 34) and Hopmann (28) have already been putting these principles into practice, it still seems important to me, that I have been able to show the 24-hours' rhythm in diabetes, thus connecting Forsgren's research work on the one hand, and its practical application on the other.

Even in the administration of insulin, the 24-hours' rhythm must be taken into accout, since its influence is of far greater importance than that of meals. In doing so, one has to bear in mind, that the same quantity of insulin may have quite a different effect according to the time of the day that it is given. Thus, in the dissimilative period much insulin will be required, whereas, during the minimum a much smaller dose will produce the same effect.

In this way the treatment of diabetes is put on a different basis, affecting both the supply of carbohydrate and the administration insulin.

Much research work still remains to be done, however, before a proper application will be possible.

Yet it is of great importance that, even now, these new principles should be accepted.

## Summary.

After a description of the technic by which, in the normal individual the 24-hours' rhythm of diuresis can be followed, the question is considered to which extent the assumptions as to the constancy of the »milieu intérieur» need to be modified. The functions of the organs show a 24-hours' rhythm, the blood is constant, whereas on the composition of the interstitial fluid no definite judgment can as yet be given.

Next an experiment is described, which is indicative for the condition present in diabetes and by which it is demonstrated that the 24-hours' rhythm in the bloodsugar, diuresis, chloride- and sugar-output can be so outspoken, that it must be seriously taken into account in the treatment of diabetes.

It is pointed out in particular, that by taking this new conception as a basis for insulin-treatment, a considerable saving of insulin can be obtained.

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## Revue des Livres:

*C. Heinemann-Grüder* und *E. Rühe:* Der Arzt in der Wehrmachtversorgung. Ärztliche Angelegenheiten der Wehrmachtfürsorge und -versorgung. Mit einem Geleitwort von Professor Dr. S. Handloser. Preis: geb. RM 6.75. Verlag von Theodor Steinkopff, Dresden und Leipzig, 1942.

Das Buch entstand unter Mitwirkung zahlreicher in Wehrmedizin und Versorgungswesen erfahrener Bearbeiter.

Das Buch beginnt mit einer übersichtlichen Darstellung der Geschichte der Versorgung beschädigter Soldaten in Preussen—Deutschland. Danach folgen Abschnitte über die Versorgungsgesetze der Wehrmacht, die Organisation der Wehrmachtversorgung, die Zusammenarbeit in Fürsorge und Versorgung und die Durchführung und Art der Heilfürsorge nach dem Wehrmachtfürsorge- und versorgungsgesetze. Zuletzt kommt ein Kapitel von 232 Seiten über Fragen der ärztlichen Beurteilung und Begutachtung. Hier werden zuerst medizinische Fragen allgemeiner Art erörtert z. B. die Zusammenhangsfrage und Sonderfragen bei der Marine und den Panzertruppen und danach einzelne Erkrankungen der verschiedenen Organsysteme kurz besprochen. Es ist selbstverständlich, dass ein Buch, das die deutschen Verhältnisse und die deutsche Organisation betreffs Wehrmachtfürsorge, Wehrmachtversorgung und was damit zusammenhängt darstellt, von grösstem Interesse für Militärärzte aller Länder sein muss.

*I. Holmgren.*

*Hans Käfer:* Feldchirurgie. 4. Auflage. 393 S. Preis: geb. RM 9:—. Verlag von Theodor Steinkopff, Dresden und Leipzig, 1942.

Das Buch ist mit einem Geleitwort vom Generaloberstabsarzt und Heeres-Sanitätsinspekteur Prof. Handloser versehen und an demselben wirken elf Oberstärzte, Oberfeldärzte, Stabsärzte, Oberstabsärzte und Generaloberstabsärzte mit. Die Darstellung ist einfach und klar. Einige der Kapitel sind nicht nur für Fachchirurgen, sondern auch für Allgemeinärzte und Internisten nützlich und lesenswert, so z. B. die Kriegswaffen und ihre Wirkung, Unterkunft, Ernährung, Behelfsvorrichtungen und praktische Winke, die Bluttransfusion u. s. w.

*I. Holmgren.*

Acta Medica Scandinavica. Vol. CXI, fasc. III, 1942.

(From the Neurologic Department, Serafimerlasarettet, Stockholm. Physician-in-chief: Professor Antoni.)

# Quinine in Extrapyramidal Morbid Conditions.

By

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(Submitted for publication March 24th, 1942).

Wolf (1) reported in 1936 that quinine had a good effect in myotonia, and this claim has since been generally accepted as correct. Quinine, administered intravenously or orally, either checks or temporarily alleviates the myotonia in myotonia congenita (Thomsen's disease) and dystrophia myotonica. Both clinical and experimental observations seem to indicate that the point of attack lies in the periphery. Kennedy and Wolf (2) demonstrated on a myotonic patient that the myotonic reaction persisted in a leg which had been completely paralyzed by means of spinal anesthesia, but that it could be made to disappear with an intravenous injection of quinine. Several workers (3, 4, 5) showed, by experiments on animals, that quinine has a complicated effect on the skeletal muscles: increased action of an isolated stimulus, decreased action of a tetanic stimulus, lessening of the irritabiliy of the motor endplate, protraction of the refractory period, antagonistic action to acetylcholine and physostigmine. Kennedy and Wolf (2) demonstrated that quinine aggravates myasthenia gravis and prostigmine aggravates myotonia.

Hassin (6), in 1939, reported good results with quinine sulphate treatment in two cases of dystonia musculorum deformans and in one case of torticollis. Lemere (7) tried the treatment in one case of dystonia musculorum deformans and likewise obtained a good

result. Hassin proceeded from the assumption that »the neurohistologic changes that have been described in a few cases of dystonia musculorum deformans are probably secondary or accidental, the motor restlessness being most likely caused, not by morphologic, but by physicochemical factors». »These are probably similar to those which are at play in myotonia congenita.» It would, therefore, seem logical to give quinine in dystonia musculorum deformans. (In view of the clinical picture in dystonia musculorum deformans, torticollis and other similar conditions, it seems scarcely probable, however, that these diseases are due solely to »physicochemical factors». I shall return to this question later. In view of Hassin's good results, it is, therefore, logical to try quinine in *all* conditions of increased muscular tone, both extrapyramidal disturbances and spastic conditions dependant on injury to the pyramidal pathways.)

Milhorat (8) recently wrote that out of eight cases of paralysis agitans, quinine had a good effect on the rigidity in two, a moderate effect in two and insignificant or no effect in four. After one to four months the effect decreased, but it returned again when the treatment was resumed, after having been stopped for a time. Scopolamine acted better on the rigidity than quinine. The injection of 1.5 mg of prostigmine resulted in a pronounced aggravation of the condition. Milhorat rightly drew the conclusion that quinine has no »specific» effect on myotonia. Probably the effect in both myotonia and paralysis agitans is the »result of the antagonistic action of the drug to cholinergic nerve stimulation».

Moss and Hermann (9) secured good results with quinine in nocturnal cramps in the calves.

At the Neurologic Department of Serafimerlasarettet, in 1938, we gave quinine to a woman with hereditary dystonia, because the morbid picture was somewhat reminiscent of myotonia. However, the treatment was stopped after only a few days, because the patient began to feel buzzing in the ears and because no improvement could be observed. Since Hassin published his findings, we have tried the quinine treatment in 23 cases exhibiting an extrapyramidal morbid picture (the patient referred to above was not included). We gave quinine sulphate per os, in doses varying between 0.50 and 2 g daily. The average dose was 1.25 to 1.50 g. The largest dose was generally given in the morning, e. g. 0.50 + 0.25 or 1 + 0.50 + 0.50 g. At least half the patients complained of

buzzing in the ears, but no other ill effects were noticed. Buzzing in the ears is rather annoying, however, and when it appeared, we reduced the dose, whereupon it usually disappeared rapidly. Some patients had the symptom with a daily dose of less than 1 g, while others tolerated 2 g a day without ill effect. With a few exceptions, which will be discussed later, no other treatment was given during the course of the quinine cure, which was continued for at least one week, and in most cases for several weeks. The few cases which improved did so within a few days.

The 23 cases treated may be divided into two groups: 5 patients with the akinetic-rigid syndrome and 18 patients with dystonic-hyperkinetic syndromes of varying natures.

*Group 1* included 2 cases of *paralysis agitans* and 3 of *postencephalitic parkinsonism*. No improvement was obtained in two cases (one of paralysis agitans and one of encephalitis chronica). A distinct but not pronounced reduction of the rigidity could be observed in two cases (one case of paralysis agitans and one of encephalitis chronica). One of these patients, a young man with very severe symptoms of postencephalitic parkinsonism, was receiving 18 mg of atropine a day at the beginning of the cure. During the treatment with quinine, the daily dose of atropine was reduced to 12 mg, but despite this a distinct improvement could be observed. In the fifth case too, which was a mild one, an improvement will probably have occurred. — Thus quinine appears to have some effect on extrapyramidal rigidity, but the substance is none too dependable, rather expensive, and not ideal as far as secondary effects are concerned. Since the publication of Milhorat's experiences with the quinine treatment in paralysis agitans (as previously mentioned, he too found a moderate, inconstant effect on the rigidity), we have given up this form of therapy, from which striking results obviously cannot be expected. However, quinine should probably be borne in mind for patients who cannot tolerate the atropine cure or the »Bulgarian cure», or in whom the results of these treatments are not satisfactory.

*Group 2* covers 7 cases of *dystonia musculorum deformans*, 7 cases of *torticollis dystonica*,[1] 3 cases of *dystonic tic* of other kinds

[1] At the Neurologic Department of Serafimerlasarettet we use the term »torticollis *dystonica*», which is probably more suitable than the older and inexact »torticollis *spastica*».

than torticollis, and 1 case of attacks of head tremor in a patient with mild (postencephalitic) parkinsonism. The etiology of most of these cases was unknown. Some of the patients had a history of uncertain encephalitis epidemica. In two sisters the dystonia was hereditary. — Three cases showed a rapid and considerable objective improvement (one case of torticollis, one of dystonia musculorum deformans and one of tic). In one case of dystonia musculorum deformans a considerable subjective but no definite objective improvement was secured. A very few cases showed insignificant subjective improvement. Thus a definite improvement was obtained in only 3 out of 18 cases, and two of these became worse again within a short time. Purely numerically, therefore, the results were rather modest, but the prognosis in these disease conditions is generally so poor that every case which shows improvement is noteworthy. The disease histories of the improved cases follow:

## Case Reports.

*Case 1.* No. 464/1940. The patient was a farmer of fifty-one with no spasmodic disease in the family. He had never had encephalitis. Since his youth and particularly during the past four years he had often had pain in the lumbar region and hips, and along the posterior aspect of the left thigh. Otherwise he had, on the whole, been healthy until the spring of 1940, when he began to have gradually increasing spasms, mainly in the right side of the trunk. Atropine treatment, with doses up to 5 mg a day, had no beneficial effect. He was admitted to the Neurologic Department of Serafimerlasarettet on September 4, 1940, five months after the onset of the spasm.

*Condition:* The spasm manifested itself as follows: When the patient lay supine in bed, which was the position he preferred, the trunk was moderately arched to the right. The left shoulder was elevated, the right depressed and pushed slightly forward. Both legs were flexed at the hips to a right angle and the feet rested flat on the mattress. The abdominal muscles on the right side, particularly in the flank, were rigidly contracted, relaxing only for a few seconds at a time and then contracting again immediately. The long spinal muscles on the right side were also strongly contracted. The right thigh was alternately flexed and extended in a somewhat irregular rhythm, so that it sometimes formed an acute angle and sometimes practically a right angle with the trunk. The pectoralis major, latissimus dorsi and trapezius muscles of the right side were also contracted time and again with no movement effect. The right arm was generally kept extended, but did not participate in the spasm. Occasionally the patient tried to check the movements of the thigh with the right hand.

The left arm and leg were not involved in the cramp. The facial expression was tense, the mouth compressed, but there was no real spasm in the face. When the patient sat up in bed, the trunk was arched to the right and somewhat rotated, so that the left shoulder was elevated and drawn backward, the right depressed and projected forward. He had to hold on with both hands, and the twitching was so violent that the whole bed shook. He was able to walk a few steps without support, with the trunk bent and twisted in the same way as when he was sitting. The right arm hung down, so that the hand reached below the knee. Occasionally he walked like an

All the figures are enlargements made from films.



*Figure 1.* Case 1.

ape, bending forward, with the right hand touching the floor (figure 2). The spasm ceased at nights, but continued unabated all day long, except for occasional interruptions of a minute or so. The picture was one of very severe and troublesome spasm.

The patient said he was at his best in the mornings, when he could walk upright, although only for a moment. He could not voluntarily suppress the spasm, but said he could cause it to abate by trying to relax and think of something else. When he was agitated the spasm increased in force. He could feed himself, though with difficulty. He said that, for a time a few months before his admission, he could cycle without difficulty, although he could not walk.

Routine examination revealed nothing of particular interest. He was a thin man with strong muscles. The internal organs were normal. The systolic pressure was 125 mm, the diastolic 80 mm. No positive neurologic findings were made, apart from the hyperkinesia. The muscular tone in the extremities was normal. The finger-nose test was normal. The patient was weak in arithmetic counting, and the memory tests were not very good,

but he showed no serious mental disturbance. He was grateful, friendly and obliging, as well as bright and alert. Eyes: the papillae were somewhat blurred, the veins ragher wide (probably not pathologically, since the condition was unchanged one year later). The Wassermann test was negative for the blood and spinal fluid. The spinal fluid was normal in other respects also. The encephalogram was normal.

The injection of 0,25 mg of scopolamine and 0,10 g of luminal afforded the patient relief for an hour or so, but led to no permanent improvement. After a few days treatment with quinine sulphate was commenced, 0,25 g being given three times daily. Within a few days the patient's condition



*Figure 2.* Case 1.

had improved in an almost dramatic fashion. The spasm would be absent for hours, if the patient rested. He could walk completely upright for a few minutes, after which the trunk began to incline slightly to the right. The dose of quinine was later increased to 1 g a day (1.2 g for a short time), but periodically the treatment had to be stopped owing to buzzing in the ears. When he was without quinine, he appeared to become worse, but not until after several days, and by no means as bad as on admission. After a few weeks the spasm described above had completely disappeared, when the patient was at rest. The abdominal and spinal muscles were relaxed. He could walk the length of the ward several times completely upright, but suddenly a violent spasm would twist the trunk to the right and he would fall helpless to the floor. As soon as he was put to bed, the spasm would disappear. As a result of these attacks, he scarcely dared to leave his bed, where he was free from trouble, except that the spasm attacked the trunk at times when he was lying on the left side. When this happened, the patient made the spasm disappear by turning over and lying on the right side. However, sometimes he had to resort to some trick, such as throwing himself against the bed or giving the bedside table a sharp blow with his

hand. Once, paradoxically enough, it wat noticed that he could walk upright, but could not sit on the bed. When he was discharged after four months, he was still unable to be up owing to the sudden spasms in the trunk.

Towards the end of the patient's stay in hospital, we also tried scopolamine, atropine, benzedrine, luminal och thiamin, either alone or combined with quinine, but no further improvement could be obtained. After his discharge, the patient took no more quinine, but his condition gradually improved. The following summer the attacks of spasm ceased. At first he crawled about, but in the autumn of 1941 he began to be able to walk upright. In December 1941 (one year after discharge) he visited the hospital. He was then able to walk completely upright. He said that, when he was tired, his trunk inclined slightly to the right. He had tried to work a little, but was unable to do much. He had a feeling of anxiety and »unpleasant thoughts», for which symptoms he is now receiving hypnotic treatment elsewhere (the improvement began before this treatment).

This was a case of severe extrapyramidal disease of unusual type. The spasm was reminiscent of both dystonia musculorum deformans and hemiballism, but probably most closely resembled the type of spasm which Stern (15) called »tetaniforme Zuckungen» in encephalitis epidemica. The disease was possibly caused by a malacia or perhaps encephalitis, localized in the basal ganglia. A considerable improvement occurred in direct connection with the commencement of medication with quinine. Later the patient improved still further and, as far as could be judged, spontaneously.

***Case 2.*** No. 372/1941. The patient was a cabinet-maker of seventythree. years of age. There was no nervous disease in the family. As a child he had »nerve fever». He had never had encephalitis lethargica and had in general always been healthy. Sixteen years previously, when he was fifty-seven, the patient began to have winking spasm and mild twitching in the cervical muscles. The cramps around the eyes increased, until he had to keep his eyes open with his fingers while reading. After one year he was treated with some sort of local injections. The spasm in the eyelids then improved and remained fairly moderate from then on. On the other hand the cramp in the neck began to progress (it was mainly manifest as a sensation of stiffness), and the patient was also affected by spasm in the lower jaw and tongue. During the succeeding years the spasm became gradually worse. Phonation and deglutition became difficult, and the patient had to confine himself to a semi-solid or liquid diet. He was admitted to the Neurologic Department on April 21, 1941, where he was under treatment for two months.

*Condition:* The patient was a bright old man in good general condition. The systolic pressure was 175, the diastolic 85. The patient managed the memory tests and simple mental arithmetic well, but ha was talkative and rambling, and the disease history was rather confused. The lower jaw performed practically incessant tonic yawning and chewing movements, during which the platysma was strongly contracted on both sides, the head was

bent somewhat forward or to one side or the other, the tongue was moved from side to side in the mouth or protruded between the lips, and the soft palate was raised and depressed in an irregular rhythm. Occasionally the eyes blinked and grunting noises were heard. The twitching increased when the patient was made the object of attention, and when he spoke (his speech was not very easy to understand, as it was rendered indistinct by

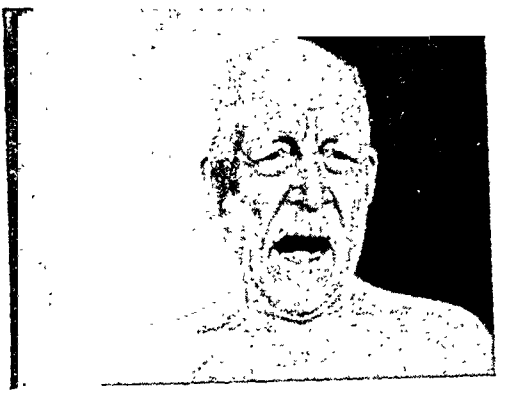


*Figure 3.* Case 2 before treatment. Note the contraction in the platysma.



*Figure 4.* Case 2 before treatment.

he cramps). Except for the spasm, neurologic examination revealed nothing of note. There was no rigidity and no other extrapyramidal symptom. The internal organs were normal. The spinal fluid was normal. The Wassermann test of the blood and blood and spinal fluid gave a negative result. Roentgen of the skull showed nothing pathological.

The patient was first treated with atropine in doses which were increased successively to 13 mg a day. He thought he improved, but no objective difference could be observed. A number of signs of intoxication developed, for which reason the atropine was stopped, and he was given no medicine at all for a few days. After that he received only quinine sulphate

per os. The largest dose given, 1+0.35 g, caused slight buzzing in the ears, but 0.50+0.35+0.35 g had no ill effects. The spasm by no means disappeared, but the movements decreased, and the pauses became longer (up to fifteen minutes). The patient could eat and speak without difficulty. The hospital barber reported that he had become much easier to shave. On only one occasion did he have a strong cramp, and that was when he was demonstrated in the lecture room.

Five months after discharge the patient came for observation. He then was having the same kind of cramps as when I first saw him, though not quite so severe. His condition had thus taken another turn for the worse. He told me that he had been relatively well for the first four months,



*Figure 5.* Case 2 after treatment.

but the twitching had never ceased entirely. He had been taking 0.50 g of quinine twice a day the whole time. A month previously the cramps had begun to increase. He then raised the dose to 0.50 g three times daily, but severe buzzing in the ears developed, and he had therefore not taken any medicine at all for a week.

This was one of the three patients with »dystonic tic». The condition was reminiscent of postencephalitic oral spasm and also of Sicard's paraspasme facial. It may be assumed that the cause of the disease in this case was arteriosclerosis or some kind of degenerative process in the basal ganglia. During the treatment with quinine, a definite and rather protracted improvement occurred, which, however, was followed by an exacerbation. Atropine had been tried without noteworthy effect.

***Case 3.*** No. 685/1941. The patient was a fisherman of forty-eight years of age with no nervous disease in the family. He had never had encephalitis lethargica nor any other diseases of interest. In June 1940 he had hit the top of his head on an iron bar. He did not faint or suffer any ill effects from the accident. In October 1940 the patient's head began to rotate to the left and somewhat backward. At first he could, with some effort, twist his head straight and to the right and keep it in these positions. The condition

gradually progressed, however, till he had great difficulty in rotating his head to the right and was unable to keep it there. He had been unfit for work for a full year. In the spring of 1941 he was treated without effect at a provincial hospital with luminal (0.10 g twice daily), atropine (4 mg daily), and with faradic current. Between August 11 and 23 1941 he was treated at the Neurologic Department of Serafimerlasarettet.

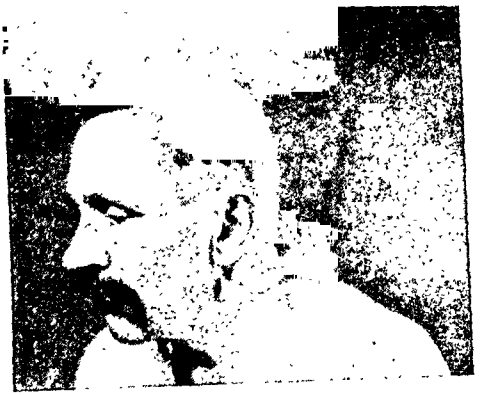


*Figure 6.* Case 3 before treatment. The last stage of an attempt to rotate the head maximally to the right, and to keep it there.



*Figure 7.* Twenty pictures, or about one second, later. The head is already on its way back to the left. Note the contracted cervical muscles.

*Condition:* The patient was a powerful man in good general condition. He was talkative and of a cheerful disposition. The head was rotated maximally to the left and held completely motionless. The right sternocleidomastoid muscle was strongly contracted. The patient could rotate his head to the right, but only with difficulty, and as if against stubborn resistance. Maximal rotation could not be achieved, and an instant later the head rotated back to the left in small jerks. If he held the nape or chin with the left hand, which he often did, and also if he raised his left arm, he could rotate his head to the front and the right and hold it quite still. If

he lifted his right arm, he could also rotate his head to the right, bur not so well as when he lifted his left arm. Otherwise no positive neurologic findings were made. The facial expression was lively and the convergence good. There was no rigidity in the extremities. All that could be noticed when the patient was walking was that the head was rotated to the left. The blood and spinal fluid gave negative Wassermann reactions. The spinal



*Figure 8.* Case 3 after treatment. Final stage of maximal rotation of the head to the right.

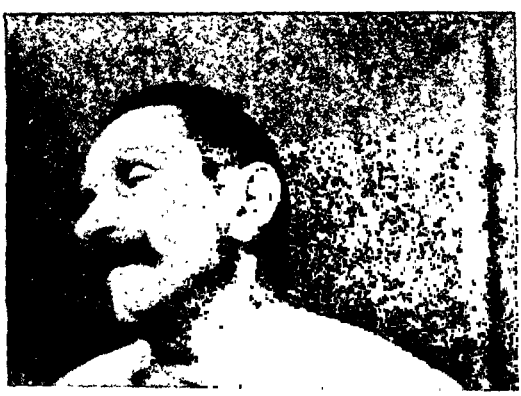


*Figure 9.* Twenty pictures, or about one second, later. The head is still rotated to the right. Actually this position could be held for more than five minutes.

fluid was normal in other respects also. A soft systolic murmur could be heard over the apex of the heart. The systolic pressure was 155 mm, the diastolic 90 mm.

*August 15, 1941.* Quinine sulphate treatment was commenced with 0.35 g twice a day.

*August 16.* The patient thought his neck felt more supple, but no objective change could be noticed.

*August 17.* The dose was increased to 0.50 g twice daily.

*August 18.* The patient was distinctly better. He could rotate his head

to the front and keep it there. Rotation to the right was easier than before. The dose was increased to 1+0.50 g.

*August 21.* Pronounced objective improvement. The head was still rotated to the left, but not more than about 45 degrees. He could keep the head rotated to the right for about five minutes at a time without the slightest twitching, and was willing to retain the position even longer. However, on rotation, he had to bend his chin down towards the right shoulder. If he rotated his head to the right with his chin up there were small twitchings to the left.

*August 23.* The patient now had slight buzzing in the ears, and the spasm was a trifle worse than on the 21st. He was so delighted with his improvement that he insisted on returning home to try to earn some money. He was discharged with 1+0.50 g of quinine.

One month later the patient wrote us that he had taken a turn for the worse, and that his condition was as before the treatment. Half a year later I saw him again. The spasm was worse than before treatment. I gave him injections of sodium chloride and told him this was a new remedy. No improvement was obtained.

This is a typical case of dystonic torticollis. A very distinct objective improvement occurred after less than one week of treatment with quinine, but proved to be only temporary. It should be borne in mind that on the second day the patient felt slightly better, although no subjective improvement was yet visible. It may perhaps be concluded from this that the patients themselves sometimes notice an insignificant improvement more readily than the physician. A young man with dystonia musculorum deformans, whom I had earlier labelled as only subjectively improved, related that he had been hospitalized fifteen times, but had never had anything as effective as quinine. I did not believe him at the time, but he may have been right. Actually it is rather difficult to judge of small changes which take place slowly in a patient whom one sees every day. It is easy to make oneself believe in an improvement which does not exist, but one may also be too critical and overlook or underestimate an improvement which really does exist. I have seen an example of this in a case of combined torticollis and head tremor. The patient did not improve with quinine. Atropine was then tried, and he said this was effective, but I could see no real difference. He left the hospital and was without medicine for a few weeks. I then saw him again, and to my amazement the twitching was double as intensive as when I had last seen him. The patient himself considered that his condition had returned to the same

point as where it was on his admission to the hospital, and it is probable that he was right. One should try to avoid mistakes of this kind by filming the patients before and after the treatment. In the case of rigidity, of course, neither films nor careful notes are of any help, and the evaluation of such cases is truly difficult.

There are several circumstances in the disease histories given above which *prove* that the central nervous system plays a dominant part, and that one cannot, like Hassin, content oneself with the assumption that »physicochemical factors» produce the spasm peripherally. As examples of these circumstances may be mentioned the paradoxal kinesias in case 1 (the patient could cycle but not walk, or could walk but not sit), the aggravation of the spasm when the patient in case 2 was demonstrated in the lecture room, and the way in which the patient in case 3 was able to check the spasm in his neck by holding his chin or nape with one hand.

The improvement in the three cases described above was quite definite and occurred a short time after the commencement of the treatment with quinine. The prognosis is admittedly poor in cases of this kind, but this does not necessarily mean that the improvement resulted from the treatment. Spontaneous remission *can* occur and probably did in case 1 after the patient's discharge from the hospital. It is also known that suggestion therapy may lead to *temporary* improvements. In view of these sources of error on the one hand, and on the other of the fact that it has been *proved* by animal experiments and clinical findings in myotonia, that quinine has an influence on muscular tone, I am inclined to conclude that the *improvement in my cases was a consequence of the treatment.* It is not so easy to explain, however, why an improvement is secured in one case, while not a trace of an effect can be observed in another apparently exactly similar, case [1]. The effect of quinine cannot be proved by suddenly replacing it with an indifferent substance for the purpose of producing an aggravation of the disease, for both Hassin's and my experiences with quinine and Burman's (10) with curare in dystonic conditions appear to show that the improve-

[1] Curare, erythroidine and quinine methochloride first affect the eyelids and external ocular muscles, then the masticatory muscles and the tongue. If the same is true of quinine, we perhaps have the explanation of the fact that the only one of my patients who had cramp in the lower jaw and tongue (No. 2) was amongst the few who improved.

ment is more prolonged than one would expect, in view of the duration of the purely pharmacological effect of these preparations. It is perhaps conceivable that one interferes in a vicious circle by giving temporarily a substance which suppresses the spasm.

It should be mentioned in passing that a few cases of *spasticity due to injury to the pyramidal pathways* were treated with quinine. It is possible that the spasticity decreased slightly in one or two cases, but I cannot vouch for it. In one case of spastic paraplegia due to vertebral metastases, there was no improvement in the troublesome spontaneous spinalautomatic spasm in the legs, while in another similar case the cramps did decrease.

To sum up, it may be said that quinine has a therapeutic effect on certain extrapyramidal morbid conditions, as Hassin and Milhorat have demonstrated. But this effect is incomplete and, above all, undependable. It would be desirable if a preparation could be found with a similar, but stronger action, and without ill effects. It may be that such a preparation already exists. While quinine has a faint curare effect, *quinine methochloride*, studied by Harvey (13, 14), is claimed to have a strong curare effect. This preparation was introduced in medical practice by Bennett (11, 12), who used it partly to preclude the complications in convulsive shock therapy, and partly in infantile spastic paralysis. Only a few short preliminary reports have been made so far, however, and it is therefore impossible to decide whether the preparation is of any practical value.

## Summary.

Altogether 23 cases with different extrapyramidal syndromes have been treated with quinine given per os. Of 5 patients with Parkinson's syndrome, 2 or possibly 3 improved, in that the rigidity decreased moderately. Of 18 patients with various dystonic-hyperkinetic syndromes, only 3 showed a definite improvement (one case of dystonia musculorum deformans, one of spasmodic torticollis, and one of »dystonic tic»). *Quinine has some therapeutic action in extrapyramidal syndromes, but it is not to be depended upon.*

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# The Hepatorenal Syndrome.

## Illustrated by a Case of Carbon Tetrachloride Poisoning.[1]

By

ERIK TRIER.

(Submitted for publication April 17, 1942).

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The following case history is a typical instance of the hepatorenal syndrome.

The patient was a tailor, 29 years old, who was admitted to Dep. C of the Copenhagen County Hospital at Gentofte for sequelæ of poisoning (carbon tetrachloride) and hepatitis (?).

*Past History:* Two years before admission the patient had a slight but typical attack of schizophrenia, for which he was admitted to Dep. 0 of the Rigshospital, where he stayed for 2 ½ months. He was treated with insulin shock, and he was found to be mentally normal at his discharge from the hospital and on reexamination one year before his present illness.

*Present Illness:* 4 days before admission the patient wanted to exterminate some moths in his upholstered furniture. For this purpose he had bought 500 g para-dichlorbenzene dissolved in 1.5 kg carbon tetrachloride. The fluid was poured into a Flit spray and the furniture was sprayed, with doors and windows closed. After he had been spraying for some length of time, his eyes began to smart and he felt unwell; still he was able — with short pauses on the balcony — to finish the spraying in 3 hours. After this he

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[1] Read before the Danish Society of Internal Medicine on February 27th, 1942.

felt very poorly and went to bed. Next morning he still felt tired and poorly; yet he was able to go to town and attend to his work, in spite of a constant sensation of oppression in the epigastrium. In the evening he had a severe headache and nausea, vomited after dinner and had to go to bed early. The following days he had some fever (up to 38.9°) and was feeling ill, with constant pain in the upper part of the abdomen, nausea and headache, but no dizziness or diarrhea. At the same time, the urination was very scanty.

On admission to the hospital, on the 4th day of illness, he complained of malaise, nausea and slight oppression in the epigastrium.

*Physical Examination:* He was quite unaffected mentally, wide awake and clear. There was slight jaundice of the skin and mucous membrane; no sign of conjunctivitis. The tongue was moist. The throat appeared normal. There was a slight tenderness to pressure in the upper part of the epigastrium, but no abnormality could be made out in the abdomen by palpation; in particular, no enlargement of the liver. The rest of the physicial examination revealed no abnormality.

*Course.* — Symptoms were rather scanty in the course of his illness: There was some nausea, and he vomited from once to 4 times a day until the 20th day of illness, and throughout the same period he complained of headache. His general condition remained strikingly good. There were no sensory disturbances throughout his illness. There was slight tenderness of the liver, which was not enlarged, until the 15th day of illness; the jaundice subsided within a week. The bowels moved spontaneously, almost daily, and the stools were normal in appearance and consistency. There was no sign of hemorrhagic diathesis. Until the 10th day of illness the output of urine was extremely scanty: 100 $cm^3$, at the most, in 24 hours. Then the urinary output rose in 6 days to no less than 3 liters. There were slight oedemata of the face, hands and legs from the 9th to the 16th day. The temperature remained normal after admission. The pulse was continually regular and strong, about 60 beats per minute. From the 20th day he felt perfectly well again.

The seriousness of the morbid condition in this case is more distinctly evident from the blood urea determinations and from the analyses of the urine, the details of which are given in Figs. 1 and 2.

The *systolic blood-pressure* was normal: 120 mm Hg on admission, then rise to maximum, 160 mm, on the 9th day of illness, followed by a gradual fall to 115 mm on the 44th day. *The diuresis* which had been very scanty even for a couple of days before admission, did not exceed 100 $cm^3$ till the 9th day. In the following days it rose abruptly, reaching in 5 days to a level of 3 liters. This sudden increase in the diuresis — the French clinicians' »crise polyurique» — — is a typical feature in the clinical picture of this condition. The

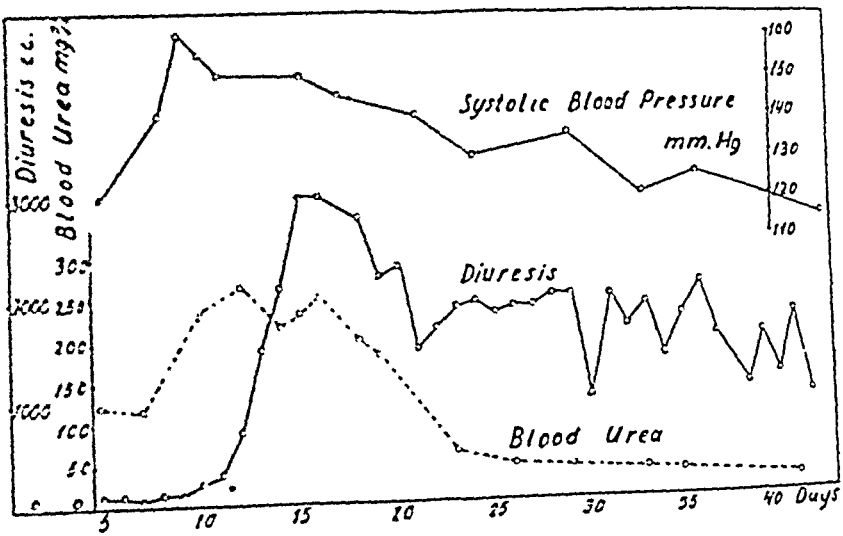



Figure 1.

diuresis then kept at a high level until the 18th day; in the remainder of his stay in the hospital it was about two liters a day. The *blood urea* concentration was 124 mg % on the 5th day of illness, and it showed no change on the 7th day, while from the 10th to the 16th day it kept at a level of about 250 mg %; then there was a fall — synchronous with the large diuresis — at first abrupt to 55 mg % in 7 days, later slow to 20 mg % in 19 days.

Fig. 2 illustrates the behavior of the diuresis. On admission there was proteinuria with a 24-hour output of 1.5 mg — corresponding to 15 $^0/_{00}$ — but then the proteinuria subsided and was all gone from the 15th day of illness. Another interesting feature is the variation of the *specific gravity of the 24-hour urine:* On admission it was about 1016, and it decreased during the following days before there was a rise in the diuresis and before the urine became protein-free; from the 11th to the 24th day it was about 1006 and for the next

twelve days, till the 36th day, it kept at a level of about 1010. In this period we were afraid that the kidneys had suffered considerable damage, even though the urea clearance showed 68 %, for the urine could be concentrated only to a specific gravity of 1012. During the following week, however, the gravity rose distinctly, and shortly before the discharge of the patient, on the 44th day of illness, the kidney function had improved a good deal, with a urea clearance of 81 % and the outcome of the concentration test showing 1017.

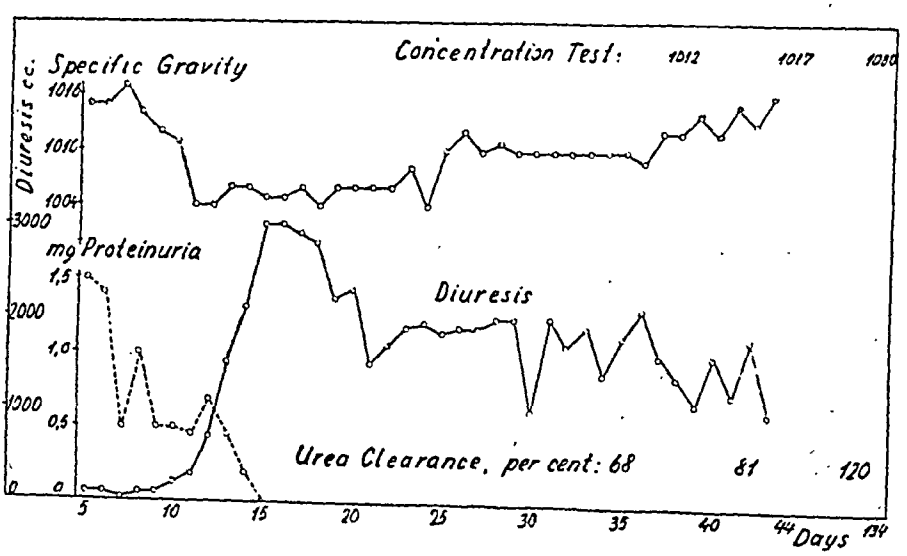



Figure 2.

On reexamination 4 months after the onset of illness the kidney function was found to be normal, with urea clearance of 120% and a concentration test showing 1030. At this time the systolic blood pressure was 130 mm, the blood urea concentration 22 mg %.

Of other examinations it is to be mentioned that microscopy of the urine (altogether 9 times) on admission showed the presence of erythrocytes and leucocytes, but no casts. Later, no erythrocytes were seen in the urine and the number of leucocytes was decreasing. On the 12th day a few granular casts were seen. On reexamination no formed elements were found in the qualitative test, and Addis' sediment count gave normal figures. The urobilin excretion was normal ($< 0.5$) on the 7th, 11th and 18th days of illness, and there was no excretion of bile pigments.

The plasma color was 30 on the 7th day, 5 on the 14th.

The hemoglobin percentage remained normal: over 100. The red blood count was 4.19, 4.50 and 4.72 million. The white blood count was 7600, 11900 and 9900. The differential count showed a normal distribution without any shift to the left in the first two counts; at the discharge there was a moderate lymphocytosis (48 %). The sedimentation rate, on admission, was 9 mm; at discharge, 2 mm. The Wassermann and Kahn tests were negative. On reexamination the hemoglobin percentage was 113, the sedimentation rate 2 mm.

*Treatment.* — The patient was given a fluid diet (fever diet with plenty of fluid); later, a lenient ordinary diet. From the 9th to the 16th day he was given 1—2 liters glucose saline subcutaneously.

## *Discussion.*

The lesion of this patient is taken to be acute carbon tetrachloride poisoning because he became ill after inhalation of vapors of this substance, and because the course of his illness is quite similar to the course of other cases of this poisoning described previously. It is possible with a fair degree of probability to exclude the diagnosis para-dichlorbenzene poisoning, for the following reasons: 1) there was no hemorrhagic diathesis; 2) there were no particular changes in the cytological composition of the peripheral blood; 3) calculation of the possible maximum — and hardly occurring — para-dichlorbenzene concentration in the air gives 4.5 mg per liter, and this figure comes near 3 mg per liter, which is the toxicity limit of this substance.

The acute carbon tetrachloride poisoning is a narcotic intoxication, which in mild cases often presents no particular features, resembling intoxication with chloroform. The clinical features of the poisoning are somewhat dependent on whether the substance is absorbed by the organism through the lungs or through the intestinal canal. In the latter case the greater part of the substance is carried directly to the liver by way of the portal circulation, and symptoms of a liver affection will most often be the predominant features. On inhalation of carbon tetrachloride the clinical features as a rule are less uniform, and the symptoms of a liver lesion are eclipsed by kidney symptoms or — to put it more cautiously — signs of abnormalities in the composition and excretion of the urine.

In cases of severe poisoning the illness commences with headache, dizziness, lassitude, fever and symptoms of mucosal irritation, involving specially the nose and conjunctivae. This onset is followed by the appearance of gastric phenomena: nausea, vomiting and diarrhea, sometimes in the form of hematemesis and melanæ. In addition, jaundice appears. During the following days the gastric symptoms remain more or less unchanged, while the jaundice is increasing, and now signs of renal damage make their appearance: oliguria, sometimes anuria, hypertension, oedema and convulsions, going on to uremia. In a few cases the poisoning has also been associated with tetany. Further, there may be cyanosis, oedema of the lungs and hemorrhagic diathesis, early as well as late. A couple of times, transitory visual disturbances have been described. Pneumonia is the most frequent complication.

If the poisoning is fatal, the patient usually dies in the second week of illness.

The *blood* may present the following abnormalities: There is an increase in the rest nitrogen content, including the urea nitrogen, in the creatinin concentration and in the amount of inorganic phosphorus. The sugar concentration is sometimes increased, sometimes lowered; the chlorine and cholesterin contents are either normal or lowered. In addition, the fibrinogen content is lowered and the guanidin content is increased. As a rule the protein content is normal, the alkali reserve normal or lowered, and the plasma color moderately increased. In a couple of cases associated with tetany the serum calcium concentration was found to be normal. There may be a brief transitory polyglobulism (resulting from concentration of the blood after repeated vomiting), sometimes followed by a hypochromic anemia. Finally, there is a moderate neutrophilic cytosis.

The *urine* is scanty, with proteinuria, and the number of formed elements is either increased but little, or the findings are similar to those seen in acute hemorrhagic nephritis. In a few cases the urine has been markedly bloody for a couple of days.

In many of the case histories reported so far, the affection has taken a course similar to that of the present case, terminating in complete recovery within a couple of weeks or months.

Table 1.

*Cases of Acute Carbon Tetrachloride Poisoning Reported in the Literature.*

| | By Mouth | Inhalation of Fumes | Total |
|---|---|---|---|
| Numbers of cases | 42 | 105 | 147 |
| Clinical symptoms of renal damage | 6 | 33 | 39 |
| History of alcoholism | 4 | 11 | 15 |
| Fatal cases | 21 | 20 | 41 |
| Autopsy reports | 19 | 8 | 27 |
| Anatomic evidence of renal damage | 12 | 7 | 19 |

As mentioned already, the symptoms depend somewhat on the way of the poisoning. This is evident from Table 1, which is the same as Smetana's Table 2 with addition of 6 cases.

It is to be pointed out in particular that there are more instances of renal damage after inhalation than after ingestion of carbon tetrachloride, and that histological changes in the kidneys have been demonstrated in nearly every fatal case of poisoning after inhalation. The frequency of alcoholism given here — the data on which undoubtedly are incomplete — is included in this tabulation because several authors state that the resistance to this form of poisoning is lowered in particular by alcoholism. For explanation of this it has been emphasized especially that alcohol promotes the absorption of carbon tetrachloride from the intestinal canal and may be the cause of a decreased glycogen content in the already damaged liver.

The pathologic-anatomical changes in the *liver* in fatal cases of acute carbon tetrachloride poisoning are often rather slight; parenchymatous and fatty degeneration, sometimes also stasis and necrosis round the bile ducts.

The *kidneys* show no distinct changes in the glomeruli (see below) but Bowman's capsule and, especially, the first convoluted tubules show so-called degenerative changes in the form of swollen vacuolized cells, which may in part be detached from the basal cells and form casts that may pluck the lumina completely. In addition, albuminous masses are seen in the lumina of the tubules. The remainder of the tubules and collecting tubes show, as a rule, merely slight, degenerative changes. Often the interstitial tissue of the cortex is oedematous, and there may be small perivascular hemorrhages. No morphological changes in the blood vessels are

seen. In two cases Smetana found some concretions in the tubules but he was not able to ascertain their chemical composition.

Carbon tetrachloride was introduced in the therapy about 20 years ago as an anthelminthic, and it has since been employed in innumerable remedies against intestinal worms, especially in the tropics. At the same time this substance found an increasing employment in numerous industrial working processes. Besides, nearly every housewife has a bottle of carbon tetrachloride in her cupboard for cleaning purposes. Furthermore, it has been used as a hairwash, and it is found in most fire extinguishers. This extensive employment of the substance was soon followed by numerous instances of poisoning, which gave rise to a great number of experimental studies on carbon tetrachloride poisoning. The attention was focussed first on the *damage to the liver*, especially because many of the experiments were carried out on dogs, which do not excrete carbon tetrachloride by way of the kidneys (in contrast to rat, guineau-pig, monkey and man). In acute moderate poisoning the damage to the liver appears in the form of degenerative globular changes with necrosis. Signs of regeneration of the liver tissue may be seen even as early as 1—2 weeks after the poisoning, and no demonstrable permanent injury to the liver results. Repeated acute or particularly severe instances of poisoning may give rise to cirrhosis with perivascular fibrosis and with sclerosis of the wall of the blood vessels. The lesion may terminate in acute yellow atrophy of the liver.

The *kidneys* may be the site of degenerative changes quite similar to the kidney changes seen in man.

In the experimental studies the *blood* and *urine* have shown quite the same abnormalities as encountered in man. It may be added that also the lactic acid content of the blood is increased and that the urine may contain considerable amounts of lactic acid in the initial stage of the hypoglycemic attacks.

### *The Hepatorenal Syndrome.*

This syndrome is nothing new. In 1842, Rokitansky found epithelial changes in the kidneys in fatal cases of acute yellow atrophy of the liver. He took these kidney changes to play a role in the production of the cerebral phenomena in the terminal stage,

which he regarded as uremia. Later this syndrome has interested especially the French clinicians, in particular after Mathieu and, at the same time, Weil in 1886 had described the infectious disease we now call Weil's disease, the most important symptoms of which are damage to the kidneys, jaundice and enlargement of the spleen. In the French literature this syndrome is still called hépatonéphrite. This designation is unfortunate though explainable, as the term nephrosis was never adopted in France, where »néphrite» is still applied to nearly all forms of medical kidney lesions. In France, in recent years, an extensive casuistic literature has been published on this subject, besides 3 monographs on »Les Hépatonéphrites»: in 1934 by Pasteur-Vallery-Radot (with which I am acquainted only through a review), in 1935 by Vague, and in 1937 by Dérot & Dérot-Piquer. These authors are fairly concordant in their definition but each employs his own nomenclature. Thus Vague divides the acute hepatonephritis into the following 4 syndromes: 1) the icteric syndrome, 2) the vasculo-hemorrhagic syndrome, 3) the toxic syndrome, 4) the biological syndrome.

The icteric syndrome requires no explanation. The vasculo-hemorrhagic syndrome comprises both early and late forms of hemorrhagic diathesis, that is, also cholemic hemorrhages, besides stasis and oedema. The toxic syndrome comprises a) nervous symptoms as delirium, convulsions, myoclonus, meningism and coma with altered type of respiration, most often in the form of Kussmaul respiration, b) intestinal symptoms, especially colicky pain and vomiting, c) cardiovascular symptoms as impairment of the heart and hypotension. The biological syndrome is divided into a) the immediate symptoms of damage to the liver and kidneys that can be recognized on analysis of the blood and urine, b) changes in the internal metabolism with abnormalities in the protein, fat, carbohydrate and salt metabolism and in the acid-base balance. The typical findings correspond precisely to the features mentioned under carbon tetrachloride poisoning. It is to be emphasized in particular that the acute stage is associated with a small diuresis, low specific gravity of the urine and slight urea output, often less than 1 g in 24 hours.

Dérot divides the acute hepatonephritis into 1) simple hepatonephritis, in which hemorrhage and severe cerebral symptoms are absent, while it practically always is accompanied by marked

azotemia (as in the case history given here), 2) hemorrhagic hepatonephritis, 3) »forme fruste», and 4) hepatonephritis with hemolytic meningeal and hydropic symptoms.

In the recent German literature the hepatorenal syndrome in carbon tetrachloride poisoning has been described thoroughly by Schütz without essential new points of view. In contrast to the above-mentioned authors, Nonnenbruch limits the designation »hepatorenal syndrome proper» to the clinical picture encountered in chronic liver lesions with pathological changes in the urine and the resulting abnormalities in the blood chemistry. He emphasizes that it may be difficult to distinguish between the parts played by the kidney and by the liver in the production of the chemical abnormalities of the blood, and that the kidney lesion often is merely functional, without any anatomical changes in the kidney. The renal damage undoubtedly results in the increase in the urea, xanthoprotein and indican concentrations of the blood, while the liver lesion causes an increase in residual nitrogen, *i. e.*, rest nitrogen minus blood urea nitrogen. The increase in residual nitrogen is attributed to disturbances in the intermediate nitrogen decomposition. The frequent present of hypochloremia may usually be differentiated from the simple hypochloremic syndrome by the faliure of the chlorine excretion to increase after intake of salt.

Nonnenbruch sets up a special form of the hepatorenal syndrome characterized by oliguria ($<$ 1000 cm$^3$ per 24 hours) with hyposthenuria without renal insufficiency, with normal or low blood urea concentration. This form is not included in the syndrome as defined by the other authors.

Nonnenbruch emphasizes that as yet we know but very little as to how and why this functional kidney disorder is started. He often finds the kidney function changing abruptly — for instance, to normal kidney function or to uremia. The kidney function is not altered by administration of pituitrin or suprarenal cortical hormone, by artificial fever after injection of sulphur or by administration of salt solution. In a few cases of cardiac insufficiency with congestion of the liver and jaundice, the injections of salyrgan are followed by the appearance of uremia — also in cases where earlier injections of salyrgan had the wanted diuretic effect.

The recent medical literature has also brought other examples of the hepatorenal syndrome in liver lesions, but I am afraid that a

great deal has escaped my attention on account of the marked variation of the nomenclature. As an example, mention is to be made of a paper by Thompson, Frazier & Rawdins (1940) on »the renal lesion in obstructive jaundice». In their 32 patients they often found proteinuria and increased blood urea. In patients who were also suffering from active or inactive chronic nephritis, the symptoms were accentuated to »cholemic nephrosis», and only these patients showed anatomical changes in the glomeruli.

**Table 2.**

*Poisonings in which the Hepatorenal Syndrome has been observed.*

| | |
|---|---|
| Phosphorus | Cincophen |
| Mercury | Picric acid |
| Lead | Trinitrotoluene (trotyl) |
| Arsenic (salvarsan) | Dinitrobenzene |
| Gold (sanocrysin) | Resorcin |
| | *Pyrocatechin* |
| Apiol | Avertin |
| Poisonous fungi | Carbon tetrachloride |
| (amanita muscaria and others) | Ethane tetrachloride (tetralin) |

As a rule, the hepatorenal syndrome is encountered only in cases of severe poisoning — in lead poisoning for instance, only in acute poisoning after intake of litharge (lead monoxide). In arsenic and gold therapy, however, it has been seen after treatment with therapeutic doses; and the same applies to administration of cinchophen and after avertin anesthesia.

**Table 3.**

*Infectious Diseases and Other Morbid Conditions in which the Hepatorenal Syndrome has been observed.*

| | |
|---|---|
| Septicemia, | Yellow fever |
| streptococcus | Epidemic hepatitis |
| staphylococcus | Malaria |
| pneumococcus | |
| perfringens | Pregnancy toxicosis |
| | Postoperative |
| Typhoid, paratyphoid | Traumatic shock |
| Leptospirosis, | Liver lesions, |
| 1. icterohæmorrhagica | hepatitis |
| 1. Sejrø | cholelithiasis |
| 1. canicolaris | cholangitis |
| | syphilis |
| Spirochæta recurrentis | cirrhosis |
| Spirochæta pallida? | cancer |
| | stasis |

In the diseases mentioned in Table 3, the syndrome is often eclipsed by other symptoms in the more severe cases — for instance cerebral and meningeal symptoms. In the leptospiroses the frequency of the syndrome varies. Vague states that it is found in 50 % of the cases of true Weil's diseases, produced by Leptospira icterohæmorrhagica, while Bukh claims that it is a rare phenomenon in infections with Leptospira canicolaris. Indeed, most of the reported cases of infection in man with the latter spirochæta have taken a mild course.

It is doubtful whether the syndrome occurs in syphilis without syphilis of the liver; presumably most instances of hepatorenal syndrome in syphilis are produced by salvarsan.

All severe cases of yellow fever are accompanied by a typical acute hepatorenal syndrome.

The term »pregnancy toxicosis» means here — in concordance with the usual nomenclature — the morbid condition occurring in the 3rd—5th months of pregnancy, also called pernicious hyperemesis. The postoperative hepatorenal syndrome is most frequent after extensive intraperitoneal operations; presumably it is often mistaken for the simple hypochloremic syndrome that is accompanied by hypotonia.

In the World War of 1914—18, the syndrome was often seen in traumatic shock. Later, in 1935, it was described again by Husfelt & Bjering, illustrated with two case histories, two severe fractures of the pelvis. The clinical picture and course of the syndrome (both cases terminated fatally) were quite in keeping with the description given here, except that nothing is said about jaundice, and no details are given concerning the liver findings. Presumably there were no macroscopic changes in the liver. Six fatal cases have been described in detail by Bywaters and collaborators and by Mayon-White & Solandt (1941). All six patients had suffered severe and extensive muscular injuries without fractures, being crushed for some length of time beneath collapsed buildings. They were treated energetically with blood and plasma transfusion, one of them also by early amputation of the crushed extremity. In spite of this treatment they all presented a gradually increasing azotemia and anuria. Jaundice was absent in these patients, too. Autopsy revealed only slight changes in the liver, namely: stasis and oedema. The kidney changes were quite like those described above. In one

of the cases the lesion was complicated by thrombophlebitis of the injured leg and by pyemia with abscesses in the kidneys; but the course of the lesion was quite like that of the non-infected.

In *chronic liver lesions*, as mentioned before, the syndrome is of a particular character, and presumably a good many clinicians will not agree with Nonnenbruch in designating every diuresis under 1000 $cm^3$ as oliguria.

In a recent review of the hypochloremic or extrarenal increase in rest nitrogen, Kaijser has incorporated especially the surgical forms of the hepatorenal syndrome into the hypochloremic syndrome. In my opinion, however, this is not justified because, as mentioned above, hypochloremia is no constant finding in the hepatorenal syndrome.

*Nature of the Renal Damage and its Place in the Systematic Classification of Medical Kidney Lesions.*

The hepatorenal syndrome furnishes an interesting contribution to the modern theory about nephritis and nephrosis being two forms of one kidney lesion, as after this theory the glomerular damage is the primary phenomenon in the pathogenesis of nephrosis, while the tubular changes are secondary and chiefly due to injury to the cells of the tubules, produced by substances that are reabsorbed from the glomerular filtrate.

After the prevailing nosography, the non-ascending medical kidney lesions are divided into glomerular nephritis and nephrosis. Typical features of the best known form of the nephroses, the genuine lipoid nephrosis, are: the presence of marked proteinuria, oliguria, hypoproteinemia, and oedema, together with the absence of hypertension, hypertrophy of the heart and terminal uremia. Transitional forms between nephritis and nephrosis — nephritis with an admixture of nephrosis — are not infrequent, however, and the differential diagnosis may be difficult. As a rule, the appearance of hypertension or hematuria sooner or later in the course of a given case will be the decisive criterion of nephritis.

In most cases of nephrosis the glomeruli show no histological abnormality in sections stained after the methods usually employed. But with the Mallory technique employed Bell for connective tissue staining the glomeruli show invariably some abnormalities in the

form of an increase in the number of endothelial cells and in the size of these cells, together with an irregular thickening of the basal membrane.

In about half of the reported case histories of carbon tetrachloride poisoning with renal damage, the injury to the kidney parenchyma has resembled the picture of an acute nephritis with hematuria, cylindruria and hypertension, although hypertension may be absent. In the rest of the cases the kidney lesion has resembled the picture of a nephrosis, meeting all the criteria or accompanied by hypertension. Presumably the marked decrease in the functional capacity of the kidney in the acute stage can be explained simply as resulting from a complete plugging of the proximal tubules as seen in fatal cases. But it is difficult later in the course of the lesion to explain the lowered kidney function as anything other than a glomerular phenomenon. Finally, I think, it would seem unreasonable to assume that the same noxious substance might produce two different kidney lesions.

In somewhat older text-books, as well as in the more recent ones on diseases of the kidney, mercury poisoning is given as an acute or necrotizing nephrosis. In severe mercury poisoning, however, the kidney lesion is not the only outstanding feature; this form of poisoning is a typical example of the »nephrotic» form of the acute hepatorenal syndrome. This designation ought to replace the term »necrotizing nephrosis», which is an unfortunate term also because necrosis in the kidneys is seen only in mercury poisoning, not in other forms of poisoning. Necrosis may likewise be absent from the kidneys in many forms of septicemia.

## *Conclusions.*

The hepatorenal syndrome may appear in severe poisoning, in severe infections, in all forms of liver lesions and in extensive deterioration of tissue. The syndrome is characterized by simultaneous affection of the liver and kidneys, presenting jaundice, oliguria and azotemia. It may be accompanied by vomiting, diarrhea, hemorrhagic diathesis and cerebral and meningeal phenomena, which may make their appearance before the manifestation of azotemia. As a rule, this syndrome is distinguished from the hypochloremic syndrome by being accompanied by

hypertension. The kidney lesion is of nephrotic type with tubular changes. The biochemical changes are variable, but hypochloremia and decreased alkali reserve are rather frequent findings.

The pathogenesis is still obscure.

The treatment is chiefly symptomatic and it is most effective when it is practicable to counterbalance the severe abnormalities in the blood chemistry.

## Summary.

Report is given of a case of acute poisoning with carbon tetrachloride through inhalation. The clinical picture of the case was dominated by dyspepsia, vomiting, jaundice, hypertension and oliguria, which was suddenly replaced by polyuria (Figs. 1 and 2). The urine contained only a few formed elements. The kidney function improved gradually and was normal again 4 months later.

The clinical aspects of carbon tetrachloride poisoning are discussed.

The case history cited here is a typical example of the acute hepatorenal syndrome (French authors: hépatonéphrite). This syndrome has been emphasized especially by French authors as a pathogenetically nosographic unity. It may arise during the course of severe poisoning with widely different substances (Table 2), in severe infections and in other morbid conditions and diseases of the liver (Table 3).

The nomenclature for this syndrome is still subject to considerable variability. Thus in text-books on kidney lesions it is called acute or necrotizing nephrosis. Other authors incorporate this condition into the hypochloremic syndrome.

The more precise details concerning the hepatorenal syndrome are still obscure. The treatment is symptomatic.

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(From the Department of Physiology, University of Uppsala, Sweden).

# On the Mechanical Impedance of the Human Thorax.

By

ERNST BÁRÁNY.

(Submitted for publication April 9th, 1942).

## The concept mechanical impedance.

As the concepts of acoustics and especially electroacoustics usually are unfamiliar to medical readers the following short explanation is perhaps not unnecessary.

Assume a very light rigid disk in contact with some part of the thorax. If this disk is acted upon by a vibrational force of sinusoidal form the movements of the disk will be determined by the force on one hand and on the other hand by the nature of the tissues under the disk. In general the disk will perform sinusoidal movements with the same frequency as the acting force. The movements will be characterized by a certain velocity and a certain phase lag between acting force and movement (fig. 1). Obviously the movements will be directly proportional to the force and inversely proportional to something which might be called the unwillingness of the thorax tissues to follow the command of the force. This unwillingness is made up by their inertia, by the stiffness of the ribs and by the viscosity of the semifluid tissue components which prevents them from yielding to the force.

The unwillingness can take the form of »non obeyance» or of »delayed obeyance» or of both. The unwillingness is termed mechanical impedance. It is expressed by two numerals: the first, called the absolute value and indicating the degree of non obeyance determines the velocity of the movement; the second, called the phase angle and indicating the degree of delay of obeyance determines the phase lag between force and movement.

The absolute value of mechanical impedance is expressed in a unit »mechanical ohm» which will be defined below. The phase angle is usually

expressed in degrees, 1° being 1/360 of a whole vibrational cycle. The phase angle is usually between + 90 and — 90 degrees. When it is negative the movements are in advance of the force. The mechanical ohm is defined by the following: If a force of 1 dyne is opposed by a resistance such that a continous movement with a velocity of 1 cm/sec. results, the magnitude of the resistance is 1 mechanical ohm. Thus if a vibrational forre of 1000 dynes acts upon a body showing a mechanical impedance of 200 mechanical ohms and 0 phase angle (200 $\underline{|0}$), the body will perform vibrations where the maximal velocity will be 1000/200 = 5 cm/sec. and the maximum of velocity will coincide with the maximum of acting force. If the

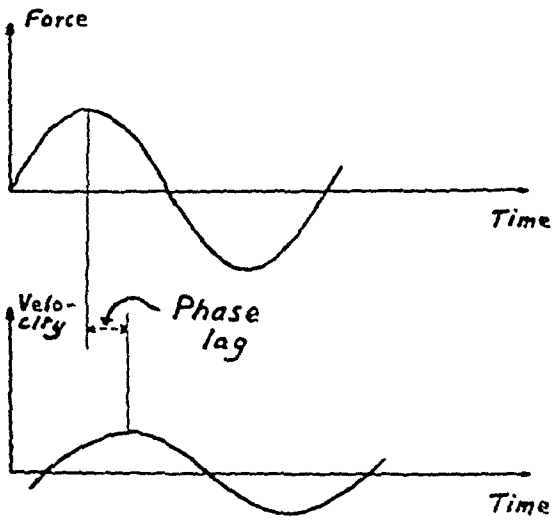



Fig. 1.

phase angle of the impedance had for instance been + 90 degrees, the maxima of velocity had occured a quarter of a period after the maxima of force. This would be the case with a pure mass. As the numerical example shows the mechanical ohm is a rather small unit. 1000 dynes is only a little more than 1 gram force and an unwillingness to move which allows a velocity of 5 cm/sec. to so small a force cannot be very serious.

## The importance of mechanical impedance for the function of the stethoscope.

Even if x-ray diagnostics play an increasing part, the use of a stethoscope still is indicated in the large majority of all cases. There can be no doubt however that the stethoscope is a very unsatisfactory instrument. Many of the sounds with diagnostical importance are heard in the stethoscope at a loudness so near to the threshold of hearing that considerable uncertainty results. In view of the extreme sensitivity of the ear this should not be necessary. There is

plenty of energy in the vibrations of the thorax and the question only is to conduct an appreciable part to the ear. This is not done with the conventional stethoscope. The reason is, that the mechanical impedance of the ears and stethoscope is very much smaller than that of the thorax wall. In acoustics as well as in electrics the maximum of energy transfer from one system to a second will be obtained when the impedances of the two systems as seen from the points of contact are of the same order of magnitude.[1] For the simple case of a galvanic cell coupled to a resistance this reduces to the well known relation external = internal resistance. For a case like the ears and stethoscope which function as external resistance to the thorax wall the mechanical impedance has to be matched to that of the thorax in the whole frequency region where good energy transmission is wanted. Obviously this must be much more difficult than the simple matching of an external resistance in the case of a galvanic cell. The first and undispensible condition is, however, that the mechanical impedance of the thorax wall is actually known. This has hitherto not been the case. The present investigation was undertaken in order to obtain information on this point.

## Measuring the mechanical impedance of the thorax wall.

The method for measuring mechanical impedance is a development from the one previously used in conjunction with the authors work on bone conduction (1938). The core of the method is a vibrator with measurable phase and amplitude (fig. 2). On a long rigid thinwalled brass tube B two coils D and R are fixed, dipping in each its own radial magnetic field from a twin pot electromagnet M, energized from the field windings F. On one side the brass tube extends for some centimeters through the lid L and ends in an interchangeable knob K. The tube with coils is suspended by two stars of steel wire W so that it is free to vibrate. When one coil is fed with alternating current the system vibrates and in the other coil an alternating electromotive force is induced, the magnitude of which is at each instant directly proportional to the velocity of the vibration. The coils are much longer than the air gap in the pot magnet

[1] The absolute magnitudes shall be identical and the phase angles of the same magnitude but with opposite signs.

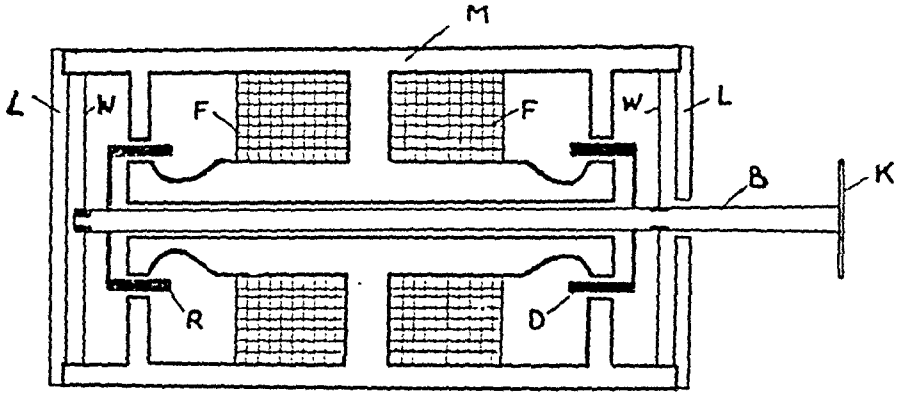



Fig. 2.

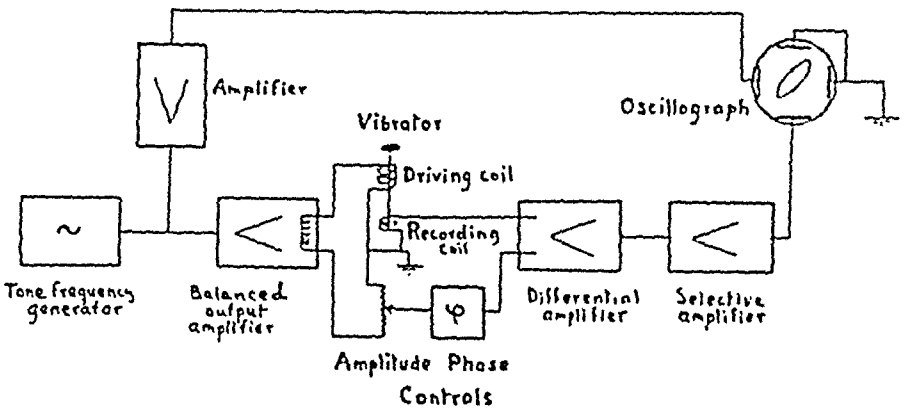



Fig. 3.

and the suspension so rigid that at all occurring pressures against the knob the number of turns in the field and herewith the sensitivity of the instrument is constant.

The induced alternating voltage is measured by compensation against a voltage derived, via phase and amplitude controls, from a resistance in series with the driving coil. As the current through this at every instance is proportional to the driving force, the compensating voltage indicates the phase and amplitude of the vibrations in relation to the driving force. This is true as long as the mass of the field magnet is so large that it does not perform appreciable vibrations. In the present case, the mass was 6 kg and no difficulties were met with down to 30 cycles per second.

As fig. 3 shows, compensation is effected with the aid of a differential amplifier working into a selective amplifier and a cathode ray tube. Deflection of the cathode ray in the other direction is made with alternating current of the same frequency, so that a

standing ellipse is seen when compensation is incomplete. The ellipse degenerates into a straight line at balance. The use of a cathode ray tube as balance indicator is preferable to an acoustic device since the latter is sensitive to stray sounds from the vibrating thorax.

The principle of measurement is very similar to the one previously used by the author. Amplitude (A) and phase ($\varphi$) of the vibrator are measured, the knob being:

1) free
2) restrained by the thorax
3) restrained by a mass of known magnitude, M.

The values obtained are labelled $A_F$, $\varphi_F$; $A_T$, $\varphi_T$ and $A_M$, $\varphi_M$ resp.

From these measurements it is easy to calculate the mechanical impedance of the thorax as seen from the knob with the aid of methods used in alternating current theory, which can not however be explained here.

If the driving force is P and the complex mechanical impedance of the free vibrator system $Z_F$, of the thorax driving point $Z_T$ and of the mass $Z_M$ the following relations hold good

$$\bar{A}_F = \frac{P}{Z_F}$$

$$\bar{A}_T = \frac{P}{Z_F + Z_T}$$

$$\bar{A}_M = \frac{P}{Z_F + Z_M}$$

where the $\bar{A}$:s are vectors.

From this one easily gets

$$Z_T = Z_M \cdot \frac{\bar{A}_M}{\bar{A}_T} \cdot \frac{\bar{A}_F - \bar{A}_T}{\bar{A}_F - \bar{A}_M}.$$

The second fraction is constructed graphically and the final value obtained by a few calculations on the slide rule.

Fig. 4 shows how a set of actual measurements is treated. M was 128 gram and the frequency 203 c. p. s.

$$\bar{A}_F = 68.6 \angle 112°$$

$$\bar{A}_T = 35.5 \angle 158°$$

$$\bar{A}_M = 10.5 \angle 120°$$

are laid out with their phases from a common origin and the tips joined in the manner shown. This gives $|\bar{A}_F - \bar{A}_T| = 51$ units and $|\bar{A}_F - \bar{A}_M| =$

$= 58.5$ units resp. and the angle $\alpha = -28°.5$ between these. ($\alpha$ is positive in the sense of rotation shown in the figure.) The length $|\bar{A}_F - \bar{A}_T|$ is divided by $|\bar{A}_F - \bar{A}_M|$ giving 0.872, this is multiplied by the ratio $\left|\frac{\bar{A}_M}{\bar{A}_T}\right| = 0.296$ and the absolute value of $Z_M = 2 \cdot \pi \cdot M \cdot \text{frequency} = 2\pi \cdot 128 \cdot 203 = 1.62 \cdot 10^5$. The result $4.2 \cdot 10^4$ is the absolute value in mechanical ohms of the mechanical driving point impedance of the thorax at this frequency. The phase angle becomes $90 + \varphi_M - \varphi_T + \alpha = +23°.5$.

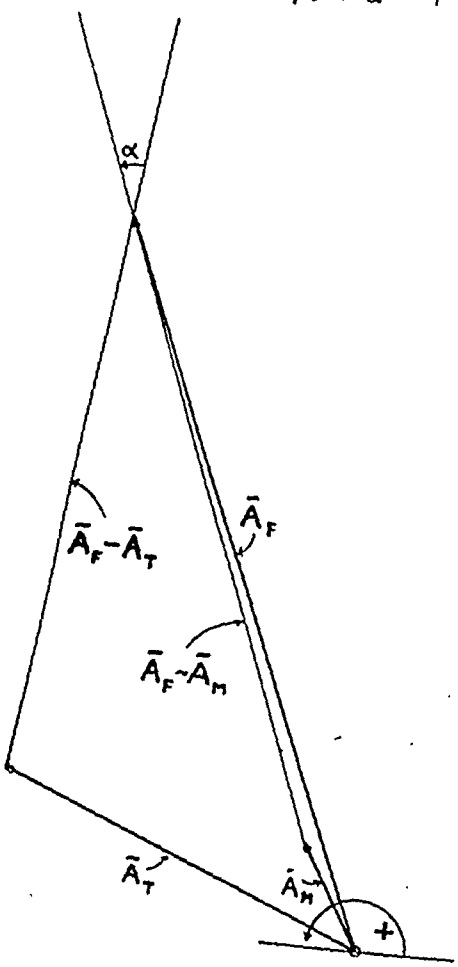



Fig. 4.

The actual arrangement was as follows: The vibrator was suspended from the ceiling on a steel wire passing over a pulley to a counterpoise. It was usually held by the subject and the knob applied with firm pressure against selected points of the thorax as perpendicularly as possible. Two plane circular knobs were used, the larger 35 mm Ø, the smaller 25 mm Ø. When the knob was in light contact with the skin the impedance was very much depending

**Table I.**

*Distribution of measured points.*

| Large knob, 35 mm Ø | | Small knob, 25 mm Ø | |
|---|---|---|---|
| Male | Female | Male | Female |
| right mamilla of A | right mamma | right mamilla of A | right mamma |
| » » » » | » » | » » » » | » » |
| region of absolute | » » | on the sternum of A at $C_4$ | |
| cardiac dullness of A: | | » » » » » » | |
| during max. insp. | | | |
| during max. exsp. | | | |
| Interscapular space of C | | | |

Frequencies used (cycles per second): 38, 53, 71, 101, 160, 203, 300, 428, 580, 800, 1160

upon the pressure, but with increasing force of application the influence of pressure rapidly diminished and at firm but in no way unpleasant pressure the influence was very slight. The force actually used was about ½ kg but of course dependent upon the diameter of the knob, being less with the smaller knob. As this is exactly what would be the case with a stethoscope no attempt at standardizing the pressure was made.

Most of the measurements were made on the thorax of A, ♂, 30 years, height 1.86 m., weight 78 kg. Some were made on the mamma of B, ♀, 21 years, height 1.67 m., weight 61 kg, nullipara. A few values were taken on the back of a second male subject, C, the knob being placed in the interscapular space. The distribution of the measurements is given by table I. The frequency interval 38—1160 c. p. s. was covered in steps of about ½ octave.

**Table II.**

*Mean mechanical driving point impedance of human thorax (in mechanical Ω).*

| Frequency interval | Knob 35 mm Ø | Knob 25 mm Ø |
|---|---|---|
| 38—71 | 30,000 $\lfloor +15°$ | 20,000 $\lfloor +50°$ |
| 101—203 | 60,000 $\lfloor +10°$ | 60,000 $\lfloor +15°$ |
| 300—580 | 70,000 $\lfloor +25°$ | 60,000 $\lfloor +5°$ |
| 800—1160 | 30,000 $\lfloor +30°$ | 20,000 $\lfloor \pm 0°$ |

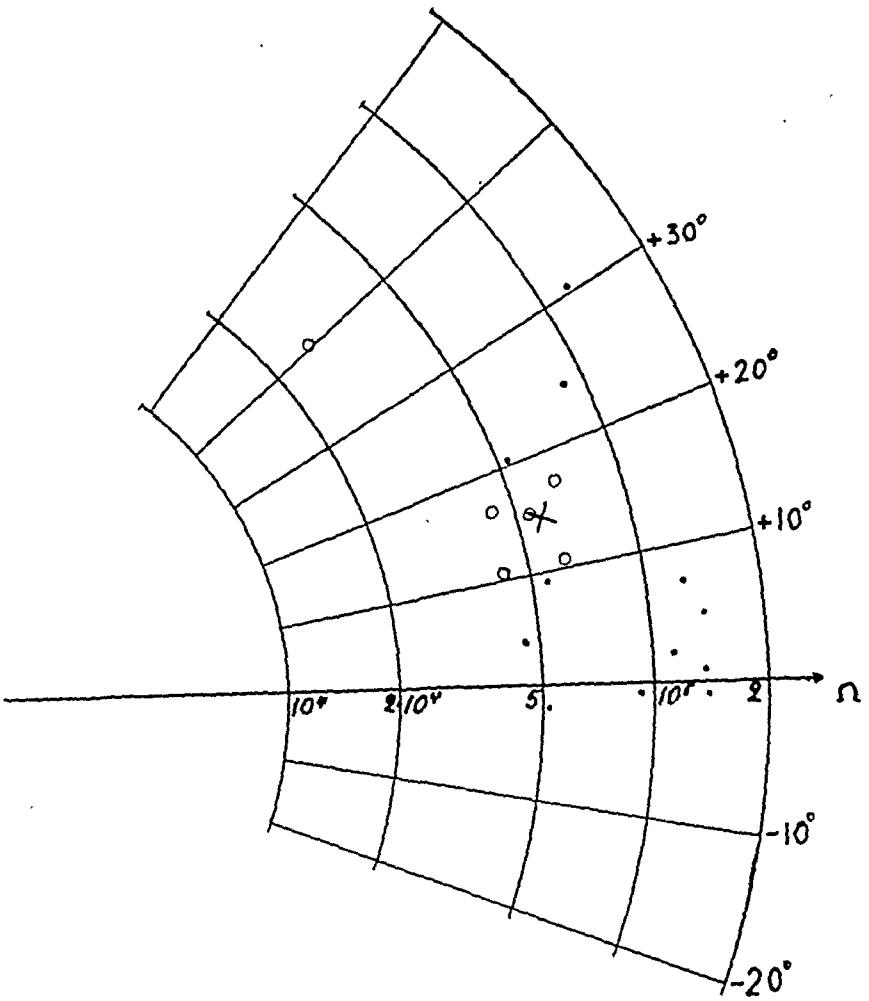



Fig. 5.

The values obtained were transferred to logarithmic polar coordinates, values referring to the same knob and a frequency interval of 1 octave being pooled. Fig. 5 serves as an example. Dots refer to subj. A, circles to B. The centers of the distributions were determined by sight. The values, shown in table II give a rough mean of the mechanical impedances that will be encountered by a stethoscope fitted with a bell or a knob of practical dimensions. A detailed analysis of the values would be without practical importance, as the same stethoscope eventually will be used on a variety of points and chests.

The implications of the values are best seen by considering that the mechanical impedance of the two ears in the frequency interval

100—1000 cycles per second is about 25—75 mechanical ohms as compared with 20000—70000 in the case of the thorax. Thus, the matching is very poor and one would expect only about $1\,^0/_{00}$ of the available energy to be transferred by a stethoscope of conventional design.

## Summary.

The importance of matching the driving point mechanical impedance of the stethoscope to that of the thorax is stressed. A method for measuring the impedance of the thorax is described and results of measurements are given. They show that the matching between a conventional stethoscope and the thorax is very poor indeed, giving a very low ratio of energy transfer.

The experiments were supported by a grant from »Svenska Sällskapet för Medicinsk Forskning» to which I want to express my gratitude.

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# Polyneuritis After Treatment with Sulfonamide Preparations.

By

EGON BRUUN and KNUD HERMANN.

(Submitted for publication March 7th, 1942.)

Sulfanilamide and its derivates applied both to animals and Man may give rise to toxic symptoms varying between slight and transitory manifestations (nausea, vomiting and diarrhea, headache, cyanosis and exanthema) and severer conditions (hepatitis, hemolytic anemia, sulfo- and methemoglobinuria, anuria), and finally, though rarely, to leukopenia which may entail agranulocytosis.

Besides causing these purely medicinal toxic symptoms, the sulfonamides have proved to possess neurotoxic properties also, and since the appearance of the preparations, a good many reports have been published of cases of peripheral mononeuritis and polyneuritis arisen after chemotherapy, particularly after treatment with uliron. Even though the neurotoxic complications never had a lethal issue — whence they cannot be classed with the catastrophal sequels — they do prolong the morbid condition so much that they must absolutely be termed serious complications.

In a recently published paper, Bieter, Beaton, Shaffer, Seery & Orr (1) study the effect of sulfanilamide and its derivates on the nervous system of chicks. The substances examined by them are

sulfanilamide, sulfapyridine, sulfathiazol, sulfamethylthiazol, sulfanilyl dimethyl-sulfanilamide, and sulfaphenylthiazol. All the preparations in the dosage applied (from 0.3 to 1.0 g per kg body weight) were able to cause neurotoxic symptoms, the intensity of which increased after the above quoted succession. Whereas nerve lesions, which were always superficial, were produced exceptionally only by the first named 3 preparations, the last named 3 preparations showed an increasing propenseness to cause lesions both in the peripheral nerves and in the central nervous system of chicks. It is true that the results of experiments on chicks cannot be applied directly to Man (chicks are, for example, not so prone to be affected toxically as are mammals; Nelson (28) thus found a less toxic effect on rabbits than on chicks) but, according to the literature reports, the neurotoxic properties of the different sulfanilamide preparations manifesting themselves in Man apparently correspond to what must be anticipated after Bieter and co-workers' chick experiments, i. e. the least toxic effects are produced by the first named 3 preparations, and gradually increasing lesions both of peripheral nerves and of the central nervous system are produced by the last named 3 preparations.

Other animal experiments with regard to the neurotoxic effect of the sulfonamides were carried out by Long & Bliss (25) who found that large doses of sulfanilamide applied to mice may give rise to bilateral vestibular dysfunction and spastic paralysis. Hagemann (15) is reported to have come to similar results, and Custer and co-workers (7) have shown that large doses of sulfanilamide applied to dogs may cause peripheral and central neurotoxic symptoms with loss of reflexes, spastic paralysis, ataxia, and blindness. Engelhardt & Hüllstrung (11) and Hüllstrung & Krause (19) with large doses of uliron were able to produce similar symptoms in pigeons, and Rosenthal (36), in fowls.

The literature treating of the neurotoxic effect of sulfanilamides on Man particularly comprises unilateral peroneus neuritis [Brun-Pedersen & Dalsgaard-Nielsen (3), Gelbjerg-Hansen & Krabbe (14), Stümpke (34), Waugh (39), and others] but also other peripheral nerves, nay, even cranial nerves, e. g. the optic nerve [Bucy (5)], the facial nerve [Bruun & Hermann (4)], may be attacked, and pharyngeal paresis is reported by van Valkenburg & von dem Borne (36).

Further, some cases of *poly*neuritis are recorded after treatment with sulfonamides, almost always after treatment with uliron, and that is one of the reasons why the uliron therapy gradually has been abandoned. These previously reported cases of polyneuritis after chemotherapy are recorded in Scheme I, which comprises 39 cases, 31 of which occurred after treatment with uliron. Among the remaining 8 are 4 cases due to sulfamethylthiazol, one case was observed after sulfathiazol, one, after sulfanilamide, one, after sulfanilamide + sulfapyridine, and one case, after sulfapyridine + sulfamethylthiazol.

From the Scheme it is evident that, in 6 out of 39 patients, there is a question of real overdosage; one patient was treated with »many tablets», and in another case nothing is known about the dosage. In the remaining 31 patients, the dosage was within the »permissible», i. e. amounting to 50 g or less.

Moreover, the Scheme shows that the lower extremities were involved in 38 out of 39 cases, the lower extremities (= L. E.) *alone* being involved in 19 cases. Only in one case were the upper extremities (= U. E.) alone involved.

Finally, Scheme I shows that, as regards the duration of the polyneuritides, several or, perhaps, many months must be reckoned with. Anything reliable about the duration of the disease cannot be said except that it has persisted longer than the time of observation which, in several cases, amounted to from 4 to 6 months.

## The authors' own cases.

Our material comprises 16 cases of polyneuritis observed after administration of sulfanilamide preparations; one of the cases, which was observed after treatment with uliron, was published before [Hermann (17)], whereas the others, all of which were observed within the last twelvemonth, occurred after some other sulfonamide treatment. This shows that toxic polyneuritis after chemotherapy is not very rare, and that other preparations than uliron may be the causal factors. Brown & Herrell (2), in a work to which we had no access, are reported to have described two cases of peripheral neuritis after treatment with sulfamethylthiazol, and Jessen (21) has described 3 such cases (cf. Scheme I). However, apart from these cases the litterature available for us does

**Scheme I.**

| Author | Sex and age | Preparation and dosage | Indication | Site of attack | Duration of illness |
|---|---|---|---|---|---|
| Brun-Pedersen & Dalsgaard-Nielsen (3) | ♂ 31 years | Uliron 50 g | Gonorrhea | U. E. | > 2 months |
| Bürger (6) | ♂ 31 years | Uliron 30 g | Gonorrhea | U. E. + L. E. | > 3 months |
| Ekbom (8) | ♂ 19 years | Uliron 28.5 g | Gonorrhea | L. E. | > 2 months |
| Fog (12) | ♂ 49 years | Uliron 20 g + streptamide 13.5 g | Gonorrhea | L. E. | > 3 months |
| Freusberg (13) I | ♀ 30 years | Uliron 32 g | Gonorrhea | U. E. + L. E. | > 18 days |
| Freusberg (13) II | ♂ 30 years | Uliron 18 g | Gonorrhea | L.E. | > 19 days |
| Gelbjerg-Hansen & Krabbe (14) | ♂ 17 years | Uliron 50 g | Gonorrhea | U.E. + L. E. | > 1 month |
| Halberg (16) | ♀ 21 years | Uliron 20 g + prontosil rubrum 6 g | Gonorrhea | U. E. + L. E. | > 5 months |
| Hofmann (18) | ♂ 24 years | Uliron 50 g | Gonorrhea | L. E. | > 2 months |
| Hüllstrung & Krause (19) | ♂ 25 years | Uliron 36 g + prontosil rubrum 4.5 g | Gonorrhea | L. E. | > 3 months |
| Jessen (21) I | ♀ 65 years | Sulfathiazol 11.5 g | Pneumonia | L. E. | > 10 days |
| Jessen (21) II | ♂ 34 years | Sulfapyridine 41 g + sulf. amethylthiazol 57.5 g | Pneumonia | U. E. + L. E. | > 6 months |
| Jessen (21) III | ♂ 63 years | Sulfamethylthiazol 73 g | Cystitis | U. E. + L. E. | > 4 months |
| Jessen (21) IV | ♂ 15 years | Sulfamethylthiazol 16 g | Osteomyelitis | U. E. + L. E. | > 6 months |
| Koch (22) | ♂ 40 years | Sulfanilamide 17.2 g + sulfapyridine 25 g | Phlegmon | r. U.E. + L. E. | about 5 months |

| | | | | | |
|---|---|---|---|---|---|
| Lembe (23) I | ♂ 20 years | Uliron 21 g | Gonorrhea | L. E. | |
| Lembe (23) II | ♂ 36 years | Uliron about 15 g | Gonorrhea | L. E. | > 2 ½ weeks |
| Lembe (23) III | ♂ 31 years | Uliron 24 g | Gonorrhea | L. E. | |
| Lembe (23) IV | ♂ 25 years | Uliron 12.5 g | Gonorrhea | L. E. | |
| Lembe (23) V | ♀ 25 years | Uliron: »many tablets» | Gonorrhea | L. E. | |
| Leroy (24) | ♂ 21 years | Uliron 36 g | Gonorrhea | r. U.E. + L.E. | > 2 months |
| Löhe, Schölzke & Zürn (26) I | ♂ 17 years | Uliron 60 g | Gonorrhea | U. E. + L. E. | > 1 month |
| Löhe, Schölzke & Zürn (26) II | ♂ 24 years | Uliron 30 g | Gonorrhea | L. E. | > 6 weeks |
| Löhe, Schölzke & Zürn (26) III | ♂ 22 years | Uliron ? g | Gonorrhea | L. E. | |
| Löhe, Schölzke & Zürn (26) IV | ♂ 28 years | Uliron 30 g | Gonorrhea | L. E. | > 1 month |
| Ornsteen & Furst (29) | ♂ 42 years | Sulfanilamide 130 g | Gonorrhea | L. E. | about 2 months |
| Radermecker (30) | ♂ 27 years | Uliron 36 g | Gonorrhea | L. E. | |
| Rost (32) I | ♂ 26 years | Uliron 30 g | Gonorrhea | U. E. + L. E. | > 4 months |
| Rost (32) II | ♂ 24 years | Uliron 30 g | Gonorrhea | L. E. | > 4 months |
| Stümpke (34) | ♀ | Uliron 15 g | Gonorrhea | U. E. + L. E. | > 6 weeks |
| Tietze (35) I | ♂ 24 years | Uliron 36 g | Gonorrhea | L. E. | |
| Tietze (35) II | ♂ 30 years | Uliron 57.5 g | Gonorrhea | U. E. + L. E. | > 1 month |
| van Valkenburg & von dem Borne (36) | ♂ 63 years | Uliron 16 g | Pyuria | U. E. + L. E. | > 4 months |
| Vermehren (37) | | Sulfamethylthiazol | Pneumonia | L. E. | |
| Wassmann (38) | ♀ 65 years | Sulfamethylthiazol 11.5 g | Pyuria | U. E. + L. E. | > 3 months |
| Wigton & Johnson (40) I | ♂ 43 years | Uliron 61 g | Gonorrhea | U. E. + L. E. | > 5 months |
| Wigton & Johnson (40) II | ♂ 22 years | Uliron 42 g | Gonorrhea | U. E. + L. E. | > 2 months |
| Wigton & Johnson (40) III | ♂ 28 years | Uliron about 60 g | C. vesicae | U. E. + L. E. | > 2 ½ months |
| Wigton & Johnson (40) IV | ♂ 67 years | Uliron 30 g | secondary pyuria | | |

Scheme

The authors'

| Pat. No. | Sex and age | Preparation and dosage | Indication | Onset of nerve symptoms *during* or *after* treatment |
|---|---|---|---|---|
| 1 | ♀ 22 years | Sulfamethylthiazol 60 g | Acne vulgaris | during |
| 2 | ♂ 28 years | Sulfamethylthiazol 40 g + dagenan-sodium 12 $cm^3$ intravenously | Pneumonia | about 2 weeks after |
| 3 | ♂ 65 years | Sulfamethylthiazol 35 g + sulfathiazol 25 g | Pyuria. Pneumonia? | about 1 week after |
| 4 | ♀ 18 years | Sulfanilamide 7.2 g | Faucial angina | during |
| 5 | ♂ 23 years | Sulfamethylthiazol 66 g | Pneumonia | 2 weeks after |
| 6 | ♂ 27 years | Sulfamethylthiazol 36 g | Sepsis? | about 3 weeks after |
| 7 | ♂ 31 years | Sulfamethylthiazol 32 g | Otitis med. supp.ac.sin. | about 1 week after |
| 8 | ♀ 28 years | Sulfamethylthiazol 32 g | Pyuria | about 1 week after |
| 9 | ♀ 26 years | Sulfamethylthiazol 42 g | Pyelitis | during |
| 10 | ♂ 60 years | Sulfamethylthiazol 64 g | Pneumonia | 1 week after |
| 11[1] | ♀ 18 years | Uliron 120 g | Fluor vag. | 1 week after |
| 12 | ♀ 61 years | Sulfamethylthiazol 50 g | Pneumonia | during |
| 13 | ♀ 35 years | Sulfathiazol 37 g | Phlebitis | about 3 weeks after |
| 14 | ♀ 61 years | Sulfamethylthiazol 42.5 g | Pneumonia | about 1 week after |
| 15 | ♀ 23 years | Sulfapyridine 10 g | Parametritis | immediately after getting up |
| 16 | ♂ 14 years | Sulfathiazol 25 g | Otitis med. ac. | about 10 days after |

[1] This case was published before [Hermann (17).]

II.

own cases.

| Site of attack | Antecedent paresthesias | Tenderness of nerves and muscles | Spinal fluid | Duration of illness |
|---|---|---|---|---|
| U. E. + L. E. | nil | nil | | > 4 months |
| U. E. + L. E. | nil | nil | | > 4 months |
| U. E. + L. E. | + | nil | 1/3, 0, 12 | > 4 months |
| U. E. + L. E. | + | nil | 3/3, 0, 10 | > 2 months |
| L. E. | nil | nil | | > 2 months |
| L. E. | nil | nil | | > 6 weeks |
| L. E. | nil | nil | | > 1 month |
| L. E. | + | nil | | > 6 weeks |
| U. E. + L. E. | nil | nil | | > 4 months |
| U. E. + L. E. | + | No tenderness of nerves; + of muscles | | > 7 months |
| U. E. + L. E. | nil | nil | 1/3, 0—1, 9 | 10 months |
| U. E. + L. E. | nil | nil | | > 5 months |
| U. E. + L. E. | nil | No tenderness of nerves; + of muscles | | > 6 weeks |
| U. E. + L. E. | nil | nil | | > 7 months |
| U. E. + L. E. | nil | nil | 0/3, 0, 16 | >24 months |
| L. E. | nil | nil | | > 6 months |

not contain any report of toxic polyneuritis after sulfamethylthiazol, and quite exceptionally only after treatment with the other sulfanilamide derivates (sulfanilamide, sulfapyridine, and sulfathiazol).

Our 16 cases of polyneuritis after treatment with sulfonamides are recorded in Scheme II. They are 9 women and 7 men, aged from 14 to 65 years. In order to avoid recording 16 fairly homonymic histories of disease, we have reported certain anamnestic and clinical data, which we think will be sufficient to cast light on every single case. A detailed description is required only with regard to a few isolated points, e. g. the reflexes.

*The reflexes.*

In one case (pat. No. 8) all the reflexes could be elicited, and they were of normal type.

The reflexes of the upper extremities were normal in 13 cases; in 2 patients (No. 4 and 14) the deep reflexes were abolished, being weakened in another patient (No. 12).

The patellar reflexes were normal in 11 cases, being abolished in 3 cases (No. 3, 4 and 12), different in 2 cases (No. 7 and 10), weakened in 1 case (No. 13).

The Achilles tendon reflexes were normal in 1 case (No. 8), being faint, almost abolished in 1 case, abolished in 12 cases (No. 1, 3, 4, 5, 9, 10, 11, 12, 13, 14, 15, 16), different in 3 cases (No. 2, 6, 7).

Cutaneous reflexes: The abdominal reflexes were normal in 12 cases, a single abdominal reflex being weakened in 2 cases (No. 1 and 14), total abolishment of abdominal reflexes being found in 2 patients (No. 4 and 11). The plantar reflexes were normal in 12 cases, being faint in 1 patient (No. 9), and abolished in 5 patients (No. 3, 5, 8, 9, 14).

Autonomous spinal reflexes: In 14 patients the Babinski reflex was negative on both sides. Two patients (No. 4 and 16) apparently presented bilateral Babinski, which we interpreted as pseudo-Babinski, and ascribed to a disturbance of the balance between agonists and antagonists (paresis of the plantar flection of the feet and toes but not of the dorsal flection). The spinal fluid of one of these patients was examined and found to be perfectly normal (see Scheme III).

*Sensibility.*

The tactile sensibility was perfectly normal in 13 cases. In 1 case was found hypesthesia-algesia of feet and crura, in 1 case, hypesthesia-algesia of both hands up to a little above the wrists and of both feet up to the middle of crura, and in 1 case, dysesthesia of the entire right hand.

Thus all the cases presented manifestations of motorial polyneuritis, the sensitive deficiency symptoms receding into the background and never occurring alone.

*The spinal fluid.*

The spinal fluid of those 4 patients who were submitted to lumbar puncture showed normal conditions, a fact which, parallelled with the other information, supports our idea of the cases being of toxic, and not of infectious, origin.

## Discussion.

As was mentioned before, the majority of the cases of polyneuritis after chemotherapy recorded in the literature have occurred after treatment with uliron, even though any preparation whatever of the sulfanilamide group *may* give rise to toxic polyneuritis. The distribution in our material is as follows:

In 9 cases polyneuritis occurred after use of sulfamethylthiazol alone;

in 2 cases, after use of sulfamethylthiazol + another chemotherapeutic;

in 2 cases, after use of sulfathiazol;
in 1 case, after use of sulfanilamide;
in 1 case, after use of sulfapyridine;
in 1 case, after use of uliron.

Our small material thus substantiates what must be anticipated after Bieter and co-workers' experiments, namely, that the neurotoxic symptoms — since the use of uliron was given up — will appear particularly after treatment with sulfamethylthiazol, and exceptionally only after administration of sulfanilamide, sulfapyridine and sulfathiazol.

*Etiology.*

There is scarcely any doubt as to the sulfonamides actually being responsible for the occurrence of the toxic polyneuritis. In those cases in which chemotherapy was instituted on account of gonorrhea, it might indeed be thought that there was a question of gonorrheal, and not of toxic, neuritis, a possibility which has been ventilated by many authors. However, gonorrheal neuritis is very rare, its clinical picture being rather different from that of toxic polyneuritis, whence the different authors deem it warrantable to assert that there has been a question of toxic polyneuritides. Even though our material need not prompt us to reflect on the differential diagnosis of gonorrheal neuritis, there might yet, in some of our cases, be a question of infectious polyneuritis. This is very improbable, however. In the first place, the polyneuritides occurred in immediate relation to chemotherapy; in the second place, they presented the typical clinical picture of toxic polyneuritis with distal, symmetric pareses and normal spinal fluid, and in the third place, the possibility of infection may in many cases be directly excluded, since infectious polyneuritis certainly is unknown after affections such as acne vulgaris and fluor vaginalis (patients 1 and 11).

*Pathogenesis.*

Thus, according to the preceding it may be considered to be highly probable that the cases described by us are due to the chemotherapy. However, in proportion to the excessive use of chemotherapy, the toxic symptoms occurring in sequel to it are so rare that one is induced to reflect on the eventual existence of predisposing or inductive factors which may play a rôle for their appearance. van Valkenburg & von dem Borne (36) thus opine that $B_1$-insufficiency should be a predisposing factor, although they fail to substantiate this assertion. Marshall, Emerson & Cutting (21) presume that there are three factors which play a decisive part for the appearance and intensity of the toxic symptoms, i. e. 1) the patient's susceptibility; 2) the dosage per kg body weight, and 3) the efficiency of the kidneys of excreting the substance. Leroy (24) finally thinks that polyneuritis often manifests itself after, or is induced by, extraordinary physical strain.

*$B_1$-insufficiency:* It was impossible to obtain complete diet

anamneses from all our patients, but none of them presented clinical signs of $B_1$-insufficiency, and the replies to our inquiries about the diet did not afford any clue with regard to deficiency of B substance in their diet. Hüllstrung & Krause (19, 20) carried out experiments on uliron-treated pigeons which received food with an admixture of $B_1$-substance, but the results of those experiments were not convincing, and Freusberg (13) does not deem it warrantable to attribute the appearance of polyneuritis to latent $B_1$-deficiency, drawing attention for example to the unreliable therapeutic effect of B-substance. Later, Engelhardt & Hüllstrung (11) caused uliron-treated pigeons to move in a revolving drum; half of the birds at the same time received B-substance, whereas the others received common food without addition of B vitamin. On termination of the experiment (which lasted 15 days) all the pigeons treated with B vitamin could fly, while the others were unable to do so. Engelhardt & Hüllstrung admit that these experiments merely show that vitamin $B_1$ may protect against pareses, and not that lack of vitamin is the cause of the toxic polyneuritides.

*The dosage:* The dosage certainly plays a part for the appearance of toxic polyneuritis, but a striking fact is that, in the great majority of the cases, it has been moderate, namely, amounting to from 30 to 36 g or, in several cases, less. This holds both for the previously reported cases and for our own material. Only in isolated cases, e. g. Ornsteen & Furst's (29) patient and our own case No. 13, was there a question of real overdosage. Our material moreover comprises patients who have received 66 g, 64 g and 60 g of sulfamethylthiazol, respectively, which must be said to be near the upper limit of the »permissible», though, subsequently, much smaller doses all of which within the generally reported dosage. That means to say that toxic polyneuritides not infrequently do occur after administration of »therapeutic» doses, nay, our patient No. 4, a previously healthy 18 year old girl, even received a very small dose, 7.2 g of sulfanilamide, which generally has but little toxic effect. Thus the capricious occurrence of polyneuritis cannot be explained satisfactorily by overdosage alone. With regard to dosage Engelhardt & Birkenmaier (9) in their experiments (see later) declare that the dose is so small »that there cannot be a question of overdosage».

Moreover, if the dosage did play a decisive rôle, a certain correlation between its magnitude and the gravity of the polyneuritis must be anticipated. That does not hold at all, however. The patient just mentioned who had received 7.2 g of sulfanilamide presented one of the most serious polyneuritides in the whole material of patients.

Scheme III.

| Dosage | Previously reported cases (cf. Scheme I) | Authors' own patients | Altogether | |
|---|---|---|---|---|
| 1—10 g | 0 | 1 | 1 | |
| 11—20 g | 8 | 0 | 8 | |
| 21—30 g | 10 | 1 | 11 | 39 cases = 76 % |
| 31—40 g | 5 | 4 | 9 | |
| 41—50 g | 6 | 4 | 10 | |
| 51—60 g | 3 | 2 | 5 | 12 cases = 24 % |
| >60 g | 4 | 3 | 7 | |
| altogether | 36 | 15 | 51 | |

In Scheme III are recorded the numbers of cases after the dosage applied. Of the 39 cases recorded in Scheme I are included 36, 3 cases being omitted, because information about the dosage was not available. From the Scheme it is evident that 39 out of 51 patients, i. e. 76 per cent, have received 50 g or less, and that 12 patients only, i. e. 24 per cent, may have been overdosed. Thus the examples quoted seem to prove adequately that the magnitude of the dosage alone cannot be the factor which is decisive of the occurrence of the polyneuritis.

*The renal function.* The efficiency of the kidneys to excrete the substance certainly may be thought to play a part as etiological factor, though it is far from being the rule that those patients who incur toxic symptoms suffer from renal insufficiency. Nearly all the cases of uliron polyneuritis were observed in young, previously healthy individuals who had received uliron treatment on account of subacute gonorrhea. It would be rather affected to assume that those young individuals should be afflicted with more or less severe renal disorders. In our material were 12 previously perfectly healthy individuals who were specially reported

never to have presented signs of kidney disease. The remaining 4 (No. 3, 10, 12, 14) were aged persons, 3 of whom with normal renal function, whereas one (No. 3), who suffered from prostata hypertrophy, had been submitted to suprapubic cystotomy with a view to subsequent prostatectomy. His blood urea was normal (18 mg %), and clearance showed 64 % of the normal, which must be considered to be the lower limit of normal variation. Nor was in any of those 16 patients found a sure reduction of the renal function. Hence, it is scarcely conceivable that reduced renal function should be the common cause of the occurrence of the toxic symptoms.

*Increased functional claims.* On the other hand, the last named possibility, namely, that the polyneuritides should become manifest after extraordinary physical strain, seems probable to us. The case of polyneuritis reported by Leroy (24) occurred after the termination of uliron treatment when the patient took an unusually long walk. Tietze (35) reports the case of a soldier who, likewise after the termination of uliron treatment, incurred polyneuritis immediately after a march past. Engelhardt & Birkenmaier (9) caused uliron-treated pigeons to move in a revolving drum during the treatment, whereas control pigeons receiving uliron at the same time were left quiet in ordinary cages. All the working pigeons incurred pareses, although the uliron doses were small, while the control pigeons failed to incur such. Later, Engelhardt & Datz (10) carried out a series of similar experiments, in which the pigeons were not placed into the revolving drum till the uliron treatment was terminated. Also in this series of experiments the working pigeons incurred pareses, while the controls remained intact. Engelhardt & Datz apply this observation to human beings and emphasize that uliron anyhow ought not to be administered to ambulant patients but that the patients if possible ought to be confined to bed until the uliron may be assumed to be excreted, i. e. about 10 days after termination of the cure. However, on the ground of Hüllstrung's studies and in order to explain the fact that some patients incur polyneuritis during their confinement to bed, Engelhardt & Datz think that it is not the work itself which causes the polyneuritis but the increased consumption of $B_1$ necessitated by the work. The

occurrence of polyneuritis in bedridden patients is explained by the fact that such patients just are confined to bed because of some complication or other, which is often attended with high fever, and such a condition also entails increased $B_1$ consumption.

On reviewing the clinical picture of toxic polyneuritis it becomes evident that crura and feet are affected in the overwhelming majority of the cases, which may support the assumption that the nerves exposed to the greatest functional demands are the easiest to be injured. Less frequently, and always less severely injured are, besides the nerves of the lower extremities, those of the upper extremities, the right hand alone sometimes being affected [Leroy (24), Hofmann (12)], sometimes the right hand at first and the left hand afterwards [Wigton & Johnson's (40) case IV, our case 14].

In all our 16 patients the lower extremities were affected, these alone being affected in 5 cases, and both lower and upper extremities, in 11 cases. However, in all these cases the paresis of the feet was more pronounced than that of the hands, for as a rule the feet showed far advanced paresis (often complete paralysis), whereas, with regard to the hands, there was mostly a question of moderate enfeeblement of the grasp of the hand, lacking opposition of the thumb, etc.

Also the previously reported cases of toxic polyneuritis preferably presented affections of the lower extremities (cf. Scheme I), whereas the upper extremities were affected more slightly or not at all. There is only one case on record in the literature in which the upper extremities alone were affected [Brun-Pedersen & Dalsgaard-Nielsen (2)]. Maybe that patient's occupation was of a kind requiring particularly great effort of his hands.[1]

Thus there is much that indicates that those parts of the body which are particularly exposed to strain are the most liable to be attacked by toxic neuritis. Another fact pointing in this direction is that the majority of the patients have incurred their

[1] In this connection another form of toxic neuritis suggests itself, namely, lead polyneuritis, the only toxic polyneuritis preferably attacking the upper extremities. This may possibly be explained by persons working with lead often being individuals who perform quite stereotype, almost convulsive movements with their hands (painters holding their brushes, typographers seizing the letters and squeezing them into the letter-case), whence they, perhaps, acquire their neuritides preferably in the upper extremities.

polyneuritides some time after discontinuation of the medication; Schaelchter (33) mentions an average latency of from 12 to 14 days, whereas Hüllstrung & Krause (19) speak of a regular »incubation time» of about 20 days.

We have not been able to demonstrate such a uniform period of latency. In 4 of our cases the neuritis developed during medication, in 12 cases, from 1 to 3 weeks after discontinuation of the medication. All these 12 patients incurred their polyneuritides after having left their beds, i. e. at a time when great mechanical exertion was required of their lower extremities. One of the 4 patients who incurred polyneuritis *during* treatment was treated ambulantly. Thus only 3 of the 16 patients incurred polyneuritis during their confinement to bed.

In this connection the anamnesis of one of our patients (No. 14) is very illustrative.

K. L., ♀ aged 61 years, admitted to the neurological department of the Kommunehospital, Copenhagen. Previously healthy. Pneumonia in 1940. In June 1941, again pneumonia, treated with sulfamethylthiazol, 42.5 g altogether in the course of 1 week. One week after suspension of the treatment, while the patient still kept her bed, she became aware of atony of both thumbs, particularly the right thumb. There were neither paresthesias nor pains. She was allowed to get up 2—3 days later. At that time she did not observe anything special but, after having been up for a couple of days, she was unable to lift her feet from the floor. She experienced neither pains nor paresthesias in her lower extremities. The pareses of the fingers gradually improved but the feet persisted paretic, whence she was admitted to the neurological department on the 29th December 1941. From August to October 1941 she had received massage treatment of the lower extremities, but without effect. Subsequently she was submitted to a series of $B_1$-injections which were likewise unsuccessful.

As regards the $B_1$-content of the patient's diet it seems to have been sufficient, for she has received from 250 to 300 $B_1$-units a day.

This instance seems to indicate clearly that the extremities which are exposed to the greatest functional requirements (the right upper extremity during confinement to bed, and the lower extremities when the patient is out of bed) are the easiest to be affected.

Besides strain there may be other inductive factors that play a rôle. Thus we have had the opportunity of treating a 53 year old sicknurse who, in July 1941, incurred a panaris on her right thumb. She was treated with warm compresses and sulfanilamide,

altogether 40 tablets = 12 g. About a fortnight later she incurred paresthesias in the median region of her right hand, typical median neuritis developing in the course of a couple of days. Another patient, a 22 year old woman, in 1931 had got some cuts on the volar side of her left wrist. Subsequently the strength of her left hand decreased and the small muscles of the hand atrophied. In July 1941 the patient was hospitalised with highly febrile pelvic peritonitis and was treated with 20 g of sulfamethylthiazol altogether. On the day after termination of the cure she incurred paresthesias in the 2 ulnar fingers of the left hand, and the neurological examination performed 3 days later disclosed typical ulnaris neuritis. It must be assumed that, in these 2 cases, there has been a question of toxic mononeuritis which has localised itself preferably in previously affected or injured nerve regions, probably because the antecedent lesions have rendered the respective nerves particularly responsive to the action of chemotherapeutics.[1]

Thus the result derived from these reflections on the pathogenesis of the sulfanilamide polyneuritis is: It cannot be excluded that patients with deficit of $B_1$ substance are particularly sensitive to chemotherapy, but this does not hold for our material of patients. Nor can renal insufficiency have played a part for the occurrence of the neuritides in our patients. Overdosage alone cannot either be the decisive causative factor. On the other hand, we are of opinion that *great functional requirements or antecedent lesions of the respective nerves may play a rôle for the occurrence of the symptoms.*

*Special Symptoms.*

From Scheme II it is evident that, in some cases, the pareses were preceded by paresthesias, as a rule of but few days' duration, in other cases they had a sudden onset without prodromes. In one of our cases (No. 10) there was moderate tenderness of the crural musculature on both sides. Nerve tenderness was not observed in any case! In several of the published cases the uliron polyneuritis was associated with muscular tenderness (Freus-

[1] These cases together with some other cases of toxic mononeuritis will be published in Nordisk Medicin [Bruun & Hermann (4)], the pathogenesis of toxic neuritis there being discussed specially.

berg, Halberg, Hofmann, Lembe, Leroy, Ornsteen & Furst, Stümpke), nay, Bürger even called his case polyneuromyositis on account of excessive muscle tenderness with edematous swelling of the crural skin. Tenderness to pressure of the affected nerves seems to be of rare occurrence. We have not met with it, whereas Lembe and Bürger have observed such cases.

*The duration of the disease.*

One of the reasons why we desired to report these cases is the immoderate prolongation of the patients' disablement due to these polyneuritides. As is evident from Scheme II we have been able to follow up only one patient (No. 11) until he was able to resume his work. Owing to his polyneuritis this patient was disabled for 10 months. At any rate it may be said that toxic polyneuritis is a complication protracting for months and months. In the 15 other cases the duration of the illness is noted as amounting to more than so many months, because we had to terminate the observation on the patients' discharge, before they were able to resume their work. In a few cases (No. 2, 9, 10, 12) we had the opportunity of submitting the patients to re-examination 4, 4, 7, and 5 months, respectively, after the inception of the polyneuritis, and they were, as yet, all unable to work. The patient No. 15 after a small dose (10 g) of sulfapyridine had incurred a polyneuritis which had persisted for more than 2 years. Her symptoms commenced immediately after the medication and had persisted essentially unchanged since then. Two years after the inception of the polyneuritis she was admitted to the neurological department of the Kommunehospital, Copenhagen, because of difficulties of gait. There was found typical polyneuritis of peripheral toxic type with reflex changes, atrophies, and atony.

Chief physician Knud H. Krabbe, M. D., told us that he considered it to be highly probable that this case had occurred as a sequel to chemotherapy; *nor* do we, on parallelling it with the other cases, find it astonishing that toxic polyneuritis despite the small dose may run so protracted a course.

*Prophylaxis.*

Partly on the ground of the present work, and partly on the ground of Bieter & co-workers' experimental investigations, we

caution against the use of sulfamethylthiazol and uliron as well as against indiscriminate administration of the remaining sulfanilamide preparations. We are of opinion that, in affections such as acne vulgaris, fluor vaginalis and pyuria, sulfonamides ought only to be resorted to as an *ultimum refugium*. Having at our disposal, for example in case of coliuria, other therapeutics which are effective in the overwhelming majority of the cases, it would seem to us to be something of a doctor's mistake to resort at once to sulfonamides, and particularly to select one of the most toxic preparations.

Patients, for instance alcoholists and diabetics, who empirically are very liable to incur neuritides, ought only to be submitted to chemotherapy in case of cogent indication. In consequence of Engelhardt & Birkemaier's experiments we advise administering to such patients plenty of B-vitamin together with the chemotherapy.

Also to patients with advanced renal insufficiency chemotherapy ought to be applied only from sheer necessity.

The patients must be confined to bed till the sulfanilamide preparation may be assumed to have been excreted.

Patients who have had nerve lesions before must be watched very carefully during and after administration of chemotherapy.

*Treatment.*

If a patient incurs premonitory paresthesias, all chemotherapy must be suspended at once, and he must be confined to bed for some time (10 days at the least), before he is permitted to expose himself to the strain of getting up. Moreover, he must be given vitamin $B_1$.

The treatment of an existing toxic polyneuritis must for the present be physiotherapy combined with liberal doses of vitamin $B_1$.

## Summary.

The authors report 16 cases of polyneuritis which has occurred in sequel to treatment with sulfanilamide preparations. Sulfamethylthiazol undoubtedly is responsible for 11 of the cases.

Physical strain seems to play a rôle as inductive factor for

the toxic polyneuritides, and previously injured nerves seem to be affected more readily than previously sound nerves.

The authors caution against the use of uliron and sulfamethylthiazol preparations as well as against indiscriminate administration of chemotherapy.

In conclusion we desire to express our thanks to those colleagues who have assisted us in collection of the material.

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# On the Prothrombin Content in Blood at Parturition.

By

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Shettles, Delfs & Hellman (1) have shown that mothers of newborn infants have higher prothrombin concentrations than the children, but they dot not state whether the concentrations in the mothers exceed those in non-pregnant women. Thordarson (2, 3) and Dam, Larsen & Plum (4) have shown that the prothrombin concentration in pregnant women are higher than in normal non-pregnant women. According to Thordarson, an increase of prothrombin begins with the third month of gravidity. Javert & Marci (5) have recently found approximately normal values at the end of pregnancy. They report that 14 per cent. of the women examined at parturition had less than 70 per cent. of normal concentrations, and they maintain that such cases indicate treatment with vitamin K. Thordarson has examined comparatively few patients only, in immediate connection with child birth.

The following paper presents a larger material of prothrombin examinations of women at parturition. A study has been made of the hyperprothrombinemia in relation to the age of the mother, the number of pregnancy, complications, loss of blood during the delivery, and the weight of the child. Thordarson's method, which was elaborated in this institute, has been applied without modifications. The values found are directly comparable with those

published by Thordarson. They were computed in relation to plasma tested against standard plasma. The 253 women examined constitute a random sample of patients in the Lying-in Hospital for Jutland, Aarhus.

The figures given for loss of blood (Table II) are largely estimated ones. Only when the hemorrhage was larger than some 400 ml was the blood collected in a graduated cylinder. It is difficult to measure the hemorrhage at a delivery, since the patient will lose some blood before a collection is possible. Addition of liquor amnii and urine may compromise the result, and hemorrhage from ruptures or episiotomy represents another difficulty. In order to check the precision of the estimates other measurements of the loss of blood were carried out in the case of a number of patients.

All collection of blood and liquid containing blood was made in a beaker. Tampons and sheets were washed with several litres of distilled water, and the rinse-water was mixed with the blood. Clotted blood was filtrated and the clots dissolved in concentratated sulphuric acid. The filtrated blood and the dissolved clots were analyzed for iron by ashing of suitable samples with concentrated sulphuric acid and concentrated nitric acid, and applying Wong's method (6). The loss of blood was computed from the measured quantity of iron and the patient's hemoglobin percentage at the delivery. (100 g hemoglobin contains 335 mg iron). The hemoglobin percentage was measured by the Sicca-method (13.8 g hemoglobin = 100 per cent.). The results of these measurements are given in Table I, and show a fair agreement between estimates and computed values, though usually the estimates of small hemorrhages are too high.

**Table I.**

*Loss of blood.*

| Estimated ml. | Computed ml. | Estimated ml. | Computed ml. |
|---|---|---|---|
| 200 | 262 | 600 | 447 |
| 900 | 1080 | 150 | 21 |
| 200 | 100 | 400 | 291 |
| 100 | 155 | 200 | 64 |
| 300 | 152 | 800 | 781 |
| 150 | 50 | 100 | 24 |
| 700 | 587 | 500 | 614 |
| 100 | 71 | 300 | 197 |
| 250 | 54 | 200 | 23 |
| 200 | 81 | | |

Table II.[1]

| No. of patient | Prothrombin % | Age of patient | No. of delivery | Albuminuria ‰ | syst. blood-pressure | No. of sutures | Estimated loss of blood | Weight of child | No. of patient | Prothrombin % | Age of patient | No. of delivery | Albuminuria ‰ | syst. blood-pressure | No. of sutures | Estimated loss of blood | Weight of child |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 310 | 185 | 21 | 1 | | | — | 300 | 3900 | 654 | 177 | 35 | 3 | | 155 | 1 | 700 | 3600 |
| 317 | 161 | 27 | 1 | | | — | 200 | 3300 | 669 | 253 | 23 | 1 | 1 | 135 | 1 | 600 | 4300 |
| 320 | 127 | 24 | 1 | 7 | 165 | — | 200 | 2200 | 684 | 206 | 28 | 1 | | | — | 100 | 3000 |
| 321 | 161 | 26 | 1 | | | — | 600 | 3800 | 685 | 173 | 38 | 1 | | | >3 E | 200 | 2800 |
| 325 | 157 | 23 | 1 | 2 | 135 | — | 500 | 3100 | 687 | 140 | 21 | 1 | | | — | 500 | 3500 |
| 328 | 218 | 43 | 7 | | | — | 300 | 3800 | 689 | 168 | 26 | 1 | | | — | 200 | 3500 |
| 332 | 144 | 22 | 1 | | | — | 100 | 3200 | 691 | 170 | 27 | 1 | | | — | 300 | 2900 |
| 334 | 253 | 34 | 3 | | | — | 200 | 3000 | 693 | 150 | 20 | 1 | | | — | 400 | 3300 |
| 353 | 218 | 24 | 1 | | | 1 | 200 | 3700 | 699 | 131 | 26 | 1 | | | >3 | 300 | 2400 |
| 354 | 170 | 22 | 1 | | | >3 | 300 | 2900 | | | | | | | | | 2600 |
| 356 | 180 | 21 | 1 | | | — | 100 | 2800 | 701 | 135 | 29 | 3 | | | — | 400 | 3600 |
| 357 | 157 | 26 | 1 | | | 2 | 300 | 3300 | 704 | 140 | 26 | 2 | | | — | 900 | 4000 |
| 359 | 210 | 23 | 1 | | | — | 700 | 3600 | 707 | 140 | 24 | 1 | | | — | 200 | 3000 |
| 360 | 173 | 30 | 1 | | | 3 | 100 | 3500 | 708 | 136 | 21 | 1 | | | — | 100 | 3100 |
| 361 | 150 | 35 | 2 | | | 3 | 300 | 4000 | 709 | 140 | 22 | 1 | | | 3 | 700 | 3000 |
| 362 | 226 | 23 | 2 | | | >3 F | 100 | 2600 | 711 | 121 | 23 | 3 | | | — | 100 | 3300 |
| 367[2] | 162 | 22 | 1 | 18 | 175 | — | 500 | 3800 | 712 | 146 | 22 | 2 | | | — | 100 | 3300 |
| 369 | 149 | 24 | 2 | | | >3 E | 200 | 3900 | 713 | 241 | 26 | 1 | | | — | 300 | 3300 |
| 371 | 136 | 25 | 1 | | | 3 | 200 | 3300 | 715 | 207 | 20 | 1 | 1 | 125 | — | 200 | 3400 |
| 373 | 180 | 18 | 1 | | | >3 E | 200 | 3100 | 716 | 208 | 23 | 1 | 3 | 180 | — | 800 | 2500 |
| 390 | 151 | 27 | 1 | | | >3 EF | 300 | 4000 | 719 | 242 | 21 | 2 | | | — | 100 | 4200 |
| 393 | 141 | 36 | 1 | | 150 | 2 | 500 | 3400 | 723 | 177 | 23 | 1 | 4 | 180 | — | 700 | 2400 |
| 397 | 122 | 24 | 1 | | | — | 200 | 2900 | 726 | 162 | 37 | 2 | | | >3 EF | 200 | 4000 |
| 401 | 195 | 31 | 2 | | | 1 | 100 | 3900 | 727 | 204 | 32 | 1 | | | — | 200 | 2300 |
| 402 | 180 | 34 | 3 | | | 1 | 100 | 3300 | 732 | 187 | 24 | 1 | | | >3 E | 300 | 3000 |
| 403 | 127 | 22 | 1 | | | — | 200 | 3500 | 735 | 144 | 26 | 1 | | | — | 900 | 3400 |
| 407 | 156 | 19 | 1 | | | 1 | 200 | 3000 | 737 | 201 | 22 | 1 | | | — | 500 | 2400 |
| 411 | 198 | 27 | 3 | | | — | 300 | 3300 | 743 | 197 | 29 | 2 | | | — | 600 | 3200 |
| 415 | 176 | 36 | 3 | | | — | 100 | 3100 | 745 | 152 | 24 | 2 | | | — | 300 | 3700 |
| 417 | 238 | 24 | 2 | | | — | 100 | 3200 | 746 | 170 | 27 | 4 | | | — | 400 | 3100 |
| 422 | 125 | 20 | 1 | 15 | 135 | — | 200 | 3400 | 747 | 140 | 25 | 2 | | | 1 | 300 | 3500 |
| 445 | 160 | 25 | 1 | 2 | 120 | — | 200 | 3400 | 753 | 100 | 26 | 1 | | | >3 | 200 | 3600 |
| 454 | 170 | 24 | 1 | 1 | 135 | — | 200 | 3900 | 755 | 139 | 30 | 2 | | | — | 100 | 3000 |
| 464 | 145 | 30 | 2 | | | — | 100 | 2900 | 758 | 128 | 33 | 3 | | | — | 1000 | 4000 |
| 468 | 156 | 26 | 1 | | | — | 100 | 2400 | 759 | 230 | 28 | 1 | | | — | 100 | 3100 |
| 469 | 140 | 26 | 2 | | | — | 400 | 3600 | 760 | 170 | 19 | 1 | | | — | 100 | 3400 |
| 482 | 136 | 39 | 5 | | | 1 | 100 | 3000 | 768 | 123 | 27 | 2 | | | — | 100 | 3300 |
| 493 | 195 | 34 | 2 | | | 1 | 100 | 2800 | 771 | 140 | 19 | 1 | | | 1 | 100 | 3000 |
| 500 | 272 | 21 | 1 | | | 1 | 200 | 2300 | 772 | 123 | 39 | 4 | | | 1 | 100 | 3600 |
| 514 | 265 | 23 | 1 | | | — | 200 | 3600 | 774 | 105 | 30 | 3 | | | — | 400 | 3600 |
| 639 | 141 | 16 | 1 | | | 2 | 400 | 3400 | 788 | 228 | 17 | 1 | | | | 200 | 2500 |

[1] Patient without sutures have presumably suffered no significant ruptures in the lower part of the vagina and the perineum. > 3 means large ruptures necessitating more than three sutures. E = episiotomy. F = forceps-delivery. Patients with > 3, E and F have usually been delivered in profound narcosis.

[2] Eclampsia.

Table II (continued).

| No. of patient | Prothrombin % | Age of patient | No. of delivery | Albuminuria ‰ | syst. blood-pressure | No. of sutures | Estimated loss of blood | Weight of child |
|---|---|---|---|---|---|---|---|---|
| 646 | 145 | 21 | 1 | | | 1 | 200 | 4100 |
| 650 | 170 | 28 | 2 | | | — | 100 | 3500 |
| 839 | 168 | 31 | 1 | | | 2 | 100 | 3000 |
| 841 | 111 | 22 | 1 | | | 1 | 200 | 3600 |
| 845 | 128 | 31 | 2 | | | — | 100 | 3100 |
| 846 | 119 | 28 | 1 | | | 3 | 1500 | 3400 |
| 851 | 255 | 30 | 5 | | | — | 600 | 4200 |
| 855 | 179 | 25 | 1 | 2 | 155 | > 3 | 300 | 2500 |
| 857 | 145 | 31 | 1 | | | — | 200 | 3200 |
| 860 | 151 | 20 | 1 | | | — | 100 | 3100 |
| 863 | 157 | 35 | 2 | | | 1 | 100 | 3200 |
| 864 | 221 | 23 | 1 | 1 | 130 | — | 200 | 2800 |
| 865 | 213 | 20 | 1 | | | — | 100 | 2800 |
| 867 | 147 | 25 | 2 | | | 3 | 200 | 3000 |
| 870 | 225 | 20 | 2 | | | 1 | 200 | 3700 |
| 874 | 157 | 19 | 2 | | | 1 | 700 | 3900 |
| 876 | 162 | 23 | 1 | | | — | 200 | 3800 |
| 877 | 157 | 35 | 5 | | | 1 | 100 | 3400 |
| 883 | 149 | 23 | 1 | | | — | 100 | 3100 |
| 884 | 178 | 27 | 2 | | | — | 200 | 3400 |
| 886 | 178 | 22 | 1 | | | 3 | 100 | 3300 |
| 888 | 157 | 20 | 1 | | | — | 100 | 3200 |
| 889 | 144 | 21 | 1 | | | 1 | 200 | 3100 |
| 890 | 113 | 19 | 1 | | | — | 1000 | 2300 |
| 894 | 139 | 20 | 1 | | | — | 100 | 2800 |
| 895 | 185 | 24 | 1 | | | 1 | 100 | 3200 |
| 896 | 139 | 33 | 3 | 1 | 120 | — | 800 | 3500 |
| 897 | 185 | 22 | 1 | 12 | 130 | 3 | 800 | 3600 |
| 898 | 149 | 27 | 1 | + | 160 | 1 | 100 | 3600 |
| 899 | 183 | 25 | 1 | | | — | 1700 | 3100 |
| 912 | 157 | 17 | 1 | | | — | 200 | 3400 |
| 913 | 136 | 22 | 3 | | | 1 | 200 | 3400 |
| 917 | 230 | 29 | 2 | | | — | 200 | 3100 |
| 918 | 248 | 18 | 1 | | | — | 200 | 3700 |
| 929 | 171 | 21 | 2 | | | — | 200 | 2800 |
| 931 | 144 | 17 | 1 | | | — | 100 | 2500 |
| 932 | 193 | 22 | 2 | 1 | 120 | — | 200 | 3700 |
| 933 | 180 | 20 | 2 | | | — | 300 | 3300 |
| 938 | 162 | 27 | 2 | | | 3 | 200 | 3900 |
| 939 | 191 | 27 | 2 | | | — | 100 | 1600 |
| 940 | 238 | 22 | 1 | | | 3 | 400 | 3200 |
| 943 | 185 | 24 | 1 | | | — | 100 | 2800 |
| 944 | 230 | 28 | 2 | | | — | 100 | 2800 |
| 945 | 166 | 30 | 1 | | | > 3 E | 300 | 3300 |
| 947 | 293 | 27 | 2 | | | — | 200 | 3200 |
| 949 | 126 | 21 | 2 | 1 | 135 | — | 200 | 3500 |
| 952 | 144 | 30 | 2 | | | 1 | 100 | 3400 |

| No. of patient | Prothrombin % | Age of patient | No. of delivery | Albuminuria ‰ | syst. blood-pressure | No. of sutures | Estimated loss of blood | Weight of child |
|---|---|---|---|---|---|---|---|---|
| 790 | 162 | 25 | 3 | . | | — | 450 | 4700 |
| 797 | 236 | 22 | 1 | 1 | 125 | — | 700 | 2400 |
| 1328 | 149 | 28 | 1 | + | 170 | — | 300 | 3500 |
| 1329 | 126 | 35 | 2 | | | — | 100 | 3300 |
| 1331 | 113 | 32 | 2 | | | — | 100 | 3500 |
| 1339 | 153 | 34 | 3 | | | — | 200 | 3600 |
| 1348 | 180 | 26 | 3 | | | — | 300 | 3800 |
| 1349 | 180 | 20 | 2 | | | — | 200 | 3200 |
| 1352 | 270 | 26 | 1 | | | > 3 E | 300 | 3200 |
| 1353 | 176 | 22 | 1 | | | — | 100 | 3300 |
| 1355 | 180 | 24 | 1 | | | 2 | 200 | 3200 |
| 1356 | 180 | 20 | 2 | | | — | 200 | 3400 |
| 1358 | 180 | 32 | 2 | | | — | 100 | 3600 |
| 1359 | 185 | 30 | 2 | | | — | 100 | 2900 |
| 1360 | 129 | 22 | 1 | | | > 3 E | 300 | 3800 |
| 1361 | 158 | 17 | 1 | | | 3 | 100 | 2700 |
| 1362 | 171 | 29 | 1 | | | — | 200 | 2900 |
| 1364 | 158 | 21 | 1 | | | — | 400 | 3700 |
| 1365 | 180 | 19 | 1 | | | > 3 EF | 800 | 3500 |
| 1372 | 153 | 29 | 2 | | | 1 | 200 | 4000 |
| 1374 | 180 | 18 | 1 | | | — | 100 | 3700 |
| 1377 | 204 | 28 | 2 | | | 3 | 400 | 3700 |
| 1383 | 171 | 22 | 2 | | | — | 100 | 2400 |
| 1386 | 201 | 20 | 1 | | | — | 100 | 3700 |
| 1388 | 186 | 25 | 2 | | | — | 200 | 3900 |
| 1389 | 171 | 27 | 1 | | | 1 | 300 | 3900 |
| 1392 | 153 | 29 | 2 | | | — | 100 | 3700 |
| 1398 | 161 | 23 | 2 | | | — | 1000 | 2600 |
| 1405 | 293 | 20 | 1 | | | 1 | 100 | 3600 |
| 1414 | 170 | 25 | 1 | 1 | 135 | — | 300 | 3100 |
| 1415 | 153 | 29 | 2 | | | — | 100 | 3600 |
| 1418 | 248 | 25 | 1 | | | 3 | 200 | 3400 |
| 1425 | 200 | 26 | 1 | | | 1 | 400 | 3100 |
| 1426 | 217 | 26 | 1 | | | — | 200 | 3000 |
| 1427 | 170 | 19 | 1 | | | — | 100 | 3100 |
| 1428 | 157 | 19 | 2 | | | — | 100 | 3800 |
| 1441 | 249 | 32 | 5 | | | — | 1000 | 4100 |
| 1442 | 282 | 24 | 1 | | | — | 200 | 2600 |
| 1445 | 171 | 21 | 1 | | | — | 100 | 3400 |
| 1450 | 153 | 26 | 1 | | | — | 100 | 3000 |
| 1451 | 167 | 26 | 2 | | | — | 400 | 4000 |
| 1463 | 156 | 20 | 1 | | | — | 300 | 2800 |
| 1464 | 167 | 30 | 7 | | | — | 200 | 3200 |
| 1465 | 114 | 27 | 2 | | | — | 100 | 3400 |
| 1466 | 156 | 33 | 3 | | | 1 | 600 | 4300 |
| 1467 | 190 | 31 | 4 | | | — | 200 | 3000 |
| 1468 | 210 | 24 | 1 | | | — | 200 | 3500 |

Table II (continued).

| No. of patient | Prothrombin % | Age of patient | No of delivery | Albuminuria ‰ | syst. blood-pressure | No. of sutures | Estimated loss of blood | Weight of child | No. of patient | Prothrombin ‰ | Age of patient | No. of delivery | Albuminuria % | syst. blood-pressure | No. of sutures | Estimated loss of blood | Weight of child |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 953 | 180 | 40 | 2 | | | — | 200 | 3000 | | | | | | | | | |
| 961 | 174 | 37 | 4 | 1 | 155 | — | 300 | 3500 | 1472 | 194 | 19 | 2 | | | — | 200 | 800 |
| 965 | 132 | 28 | 1 | | | 2 | 100 | 3500 | 1473 | 194 | 30 | 2 | | | — | | 1000 |
| 966 | 132 | 25 | 1 | 2 | 165 | 3 | 200 | 5000 | 1478 | 99 | 22 | 3 | 16 | 135 | — | 200 | 3900 |
| 967 | 179 | 25 | 1 | | | 1 | 200 | 3800 | 1479 | 243 | 35 | 6 | 2 | 120 | > 3 E | 900 | 3200 |
| 969 | 174 | 23 | 1 | | | — | 300 | 2900 | 1480 | 253 | 28 | 1 | | | 2 | 100 | 4100 |
| 970 | 191 | 21 | 1 | | | — | 100 | 3200 | 1481 | 225 | 18 | 1 | | | 1 | 200 | 3100 |
| 1318 | 174 | 24 | 2 | | | > 3 E | 300 | 3700 | 1483 | 180 | 18 | 1 | | | — | 100 | 2900 |
| 1319 | 131 | 19 | 1 | | | — | 100 | 2700 | 1487 | 135 | 20 | 1 | | | — | 100 | 2900 |
| 1322 | 176 | 29 | 1 | | | > 3 E | 200 | 3400 | 1488 | 99 | 20 | 1 | | | — | 200 | 3200 |
| 1490 | 131 | 36 | 2 | | | — | 100 | 4200 | 1780 | 160 | 21 | 1 | | | > 3 E | 200 | 3400 |
| 1519 | 264 | 28 | 1 | | | — | 100 | 3200 | 1786 | 149 | 28 | 1 | | | — | 200 | 3500 |
| 1527 | 230 | 37 | 6 | | | — | 300 | 4200 | 1788 | 166 | 18 | 1 | | | — | 600 | 4100 |
| 1529 | 157 | 24 | 2 | | | — | 100 | 3500 | 1791 | 221 | 17 | 1 | ¾ | 120 | — | 1700 | 3400 |
| 1530 | 157 | 27 | 1 | | | 2 | 100 | 300 | 1792 | 145 | 21 | 1 | 4 | 120 | — | 150 | 2900 |
| 1564 | 132 | 33 | 3 | | | — | 100 | 3400 | 1794 | 162 | 19 | 1 | 7 | 120 | — | 400 | 3800 |
| 1567 | 157 | 30 | 2 | | | 2 | 200 | 4000 | 1872 | 166 | 21 | 1 | | | — | 200 | 3300 |
| 1570 | 157 | 21 | 1 | | | — | 200 | 3500 | 1875 | 140 | 20 | 2 | | | 1 | 100 | 4100 |
| 1579 | 170 | 22 | 1 | | | 1 | 100 | 3300 | 1876 | 196 | 28 | 1 | | | — | 100 | 4400 |
| 1580 | 217 | 30 | 1 | 1 | 135 | 2 | 100 | 3600 | 1877 | 166 | 20 | 2 | | | — | 500 | 3600 |
| 1587 | 145 | 18 | 1 | | | — | 600 | 3700 | 1878 | 149 | 22 | 2 | | 155 | 2 | 1200 | 2800 |
| 1589 | 123 | 30 | 1 | | | 3 E | 200 | 3600 | 1879 | 230 | 28 | 1 | | | > 3EF | 600 | 3400 |
| 1590 | 277 | 24 | 1 | | | — | 700 | 4100 | 1880 | 225 | 23 | 1 | ¾ | 135 | 2 | 400 | 4000 |
| 1593 | 157 | 19 | 1 | | | — | 100 | 2300 | 1881 | 144 | 26 | 1 | | | 2 | 200 | 3500 |
| 1595 | 276 | 21 | 1 | | | — | 200 | 3500 | 1886 | 157 | 23 | 2 | | | — | 500 | 4300 |
| 1596 | 276 | 30 | 1 | | | — | 100 | 3000 | 1888 | 139 | 28 | 3 | | | — | 100 | 3700 |
| 1597 | 162 | 27 | 1 | | | — | 100 | 2500 | 1891 | 132 | 28 | 2 | | | — | 200 | 3300 |
| 1598 | 85 | 18 | 1 | | | — | 200 | 3200 | 1892 | 123 | 32 | 1 | | | 1 | 500 | 4000 |
| 1603 | 196 | 21 | 2 | | | — | 400 | 3300 | 1893 | 128 | 23 | 1 | | | — | 100 | 2600 |
| 1604 | 196 | 26 | 1 | | | 1 | 1000 | 4000 | 1895 | 187 | 30 | 3 | | | 1 | 100 | 2100 |
| 1605 | 170 | 24 | 2 | | | 2 | 100 | 3300 | 1896 | 170 | 36 | 2 | | | 1 | 200 | 3000 |
| 1742 | 152 | 22 | 1 | | | — | 200 | 3600 | 1898 | 185 | 31 | 2 | | | — | 100 | 3300 |
| 1753 | 93 | 24 | 1 | 3 | 130 | — | 900 | 3600 | 1899 | 162 | 24 | 3 | | | — | 100 | 3300 |
| 1755 | 167 | 23 | 1 | | | — | 200 | 3500 | 1905 | 166 | 29 | 2 | | | 2 | 100 | 4100 |
| 1758 | 128 | 19 | 1 | | | — | 100 | 3500 | 1910 | 187 | 28 | 2 | | | 1 | 200 | 4200 |
| 1759 | 160 | 22 | 1 | | | — | 300 | 3200 | 1911 | 162 | 19 | 1 | | | 3 | 500 | 4200 |
| 1767 | 155 | 22 | 1 | | | — | 150 | 3100 | 1912 | 190 | 20 | 2 | | | — | 300 | 3200 |
| 1769 | 150 | 19 | 1 | | | — | 700 | 3200 | 1913 | 185 | 26 | 2 | | | — | 300 | 3700 |
| 1771 | 124 | 23 | 1 | | | — | 100 | 1800 | 1914 | 125 | 18 | 1 | | | — | 400 | 4300 |
| 1778 | 167 | 17 | 1 | | | — | 250 | 3200 | | | | | | | | 300 | 2800 |

The complete material is presented in Table II. It comprises 253 women, in whom the prothrombin concentration was determined at parturition. A frequency distribution of the values found is shown in Table III.

Table III.

| Prothrombin per cent. at parturition. | No. of women. |
|---|---|
| 60— 99 | 4 |
| 100—139 | 42 |
| 140—179 | 118 |
| 180—219 | 54 |
| 220—259 | 25 |
| 260—299 | 10 |
| Total | 253 |
| Mean prothrombin per cent .. | 173 |
| Standard deviation ..... | 42 |
| Standard error of the mean .. | 2.6 |
| Highest value: 293 %; lowest value:..... | 85 % |

For comparison it should be noted that by examinations of 47 non-pregnant, normal women Thordarson found a mean concentration of 101 ± 1 per cent., and a standard deviation of 8 per cent., the values ranging from 85 to 116 per cent.

The distribution shown in Table III is markedly right-skewed, and the dispersion is strikingly larger than that of normal, non-pregnant women. Very few of the parturients had normal concentrations, and no case of hypoprothrombinemia was found. The high prothrombin concentrations undoubtedly explain the high velocity of blood coagulation at the end of pregnancy found by several investigators, cf. Kühnel (7).

Table IV[1]

| Period | No. of women examined | Prothrombin per cent mean | Standard deviation | Standard error of the mean |
|---|---|---|---|---|
| 1/3 —31/3 ..... | 36 | 170 | 31 | 5.2 |
| 1/4 —31/5 ..... | 47 | 172 | 42 | 6.2 |
| 5/6 —26/6 ..... | 54 | 173 | 39 | 5.3 |
| 27/8 —16/9 ..... | 37 | 178 | 38 | 6.2 |
| 16/9 —17/10 ..... | 41 | 181 | 43 | 6.7 |
| 14/11—16/12 ..... | 38 | 164 | 29 | 4.7 |

[1] 32 parturients examined 29/1—10/2-42 had a mean prothrombin concentration = 161 %.

The examinations took place through the period March-December 1941. In Table IV mean concentrations have been computed for six sub-periods.

It appears from this Table (IV), that the means increase through the summer and decline to lowest value in November-December. Thordarson examined 25 women at parturition, and found a mean concentration of 153 per cent. The majority of these examinations were carried out during the months December-January, and this may account for his having found a somewhat lower mean concentration, than we did. At present, however, the apparent seasonal variation in the prothrombin concentration at parturition cannot be regarded as established. The difference between the mean values in Table IV is not statistically significant.

Table V.

| Prothrombin per cent | Age of mother (year) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 15—19 | 20—24 | 25—29 | 30—34 | 35—39 | 40—44 | Total |
| 60— 99 | 1 | 3 | — | — | — | — | 4 |
| 100—139 | 4 | 14 | 11 | 9 | 4 | — | 42 |
| 140—179 | 18 | 45 | 35 | 10 | 10 | — | 118 |
| 180—219 | 5 | 22 | 14 | 11 | — | 2 | 54 |
| 220—259 | 4 | 9 | 7 | 3 | 2 | — | 25 |
| 260—299 | — | 6 | 3 | 1 | — | — | 10 |
| Total | 32 | 99 | 70 | 34 | 16 | 2 | 253 |
| Mean | 169 | 175 | 175 | 173 | 160 | 200 | 173 |
| Standard deviation | 37 | 46 | 40 | 43 | 36 | — | 42 |
| Standard error of the mean | 7 | 5 | 5 | 7 | 9 | — | 3 |

Table V shows that the average prothrombin concentrations are of the same order of magnitude in different age-groups.

A classification according to the number of parturition shows no significant differences in mean prothrombin concentrations, cf. Table VI.

That nephropathy, the most frequent complication in the last period of pregnancy, plays no part either, appears from Table VII, which comprises 27 cases of nephropathia gravidarum (patients

Table VI.

| Prothrombin per cent | Parity | | | Total |
|---|---|---|---|---|
| | 1 | 2 | 3 and higher | |
| 60— 99..... | 3 | — | 1 | 4 |
| 100—139..... | 23 | 9 | 10 | 42 |
| 140—179..... | 73 | 34 | 11 | 118 |
| 180—219..... | 29 | 19 | 6 | 54 |
| 220—259..... | 15 | 5 | 5 | 25 |
| 260—299..... | 9 | 1 | — | 10 |
| Total | 152 | 68 | 33 | 253 |
| Mean ..... | 175 | 174 | 165 | 173 |
| Standard deviation | 44 | 33 | 45 | 42 |
| Standard error of the mean ..... | 4 | 4 | 8 | 3 |

with albuminuria $\geqq$ 1 per mille, or patients with less albuminuria, buth with hypertension).

The only patient in the material suffering from eclampsia (No. 367) had normal increase of prothrombin.

There is nothing to indicate that relatively low prothrombin concentrations are related to large hemorrhages in connection with

Table VII.

*27 Cases of Nephropathy*

| Prothrombin per cent | No. of Cases | Prothrombin per cent | No. of Cases |
|---|---|---|---|
| 80— 99 | 1 | 180—199 | 3 |
| 100—119 | — | 200—219 | 3 |
| 120—139 | 5 | 220—239 | 2 |
| 140—159 | 5 | 240—259 | 2 |
| 160—179 | 6 | | |
| | | Total | 27 |
| Mean ..... | | 173 per cent | |
| Standard deviation ..... | | 36 » » | |
| Standard error of the mean ..... | | 5 » » | |

parturition. In view of the lack of precision in the estimates for hemorrhage, two groups only have been compared, viz. patients who lost som 100 ml of blood, and patients with a hemorrhage af about 600 ml or more, cf. Table VIII. This comparison does not include patients who were delivered in profound narcosis because of episiotomy or episiotomy in connection with forceps-delivery. Patients suffering large ruptures, necessitating more than three sutures, were also omitted.

Table VIII.

| Prothrombin per cent | Hemorrhage 100 ml | Hemorrhage 600 ml and large |
|---|---|---|
| 80— 99 | — | 2 |
| 100—119 | 1 | 2 |
| 120—139 | 17 | 2 |
| 140—159 | 22 | 7 |
| 160—179 | 17 | 6 |
| 180—199 | 13 | 4 |
| 200—219 | 4 | 2 |
| 220—239 | 5 | 1 |
| 240—259 | 1 | 3 |
| 260—279 | 2 | — |
| 280—299 | — | — |
| Total | 82 | 29 |
| Mean | 168 | 169 |
| Standard deviation | 34 | 43 |
| Standard error of the mean | 4 | 8 |

It appears from Table IX that there is no evidence whatsoever of a relationship between the weight of the child and the prothrombin concentration of the mother.

Thus the inquiry has shown that the prothrombin concentration of the blood at parturition is considerably higher than the value found in normal non-pregnant women. The mean concentration was 173 per cent, but there is a considerable dispersion. The mean values for patients examined in August, September and October were slightly higher than that for patients examined in November-December. Remarkably low concentrations were found in five patients (753, 1478, 1488, 1598 and 1753). Two of these only

Table IX.

| Prothrombin per cent | Weight of child (g) | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | —2000 | 2000—2300 | 2400—2700 | 2800—3100 | 3200—3500 | 3600—3900 | 4000—4300 | 4400— | |
| 60— 99 | — | — | — | — | 3 | 1 | — | — | 4 |
| 100—139 | 1 | 3 | 2 | 7 | 17 | 7 | 3 | 2 | 42 |
| 140—179 | — | 1 | 9 | 26 | 44 | 22 | 14 | 2 | 118 |
| 180—219 | 2 | 1 | 2 | 15 | 14 | 17 | 3 | — | 54 |
| 220—259 | — | — | 3 | 7 | 6 | 2 | 7 | — | 25 |
| 260—299 | — | 1 | 1 | 1 | 4 | 2 | 1 | — | 10 |
| Total | 3 | 6 | 17 | 56 | 88 | 51 | 28 | 4 | 253 |
| Mean | 173 | 167 | 175 | 181 | 169 | 174 | 184 | 140 | 173 |
| Standard deviation | — | — | 43 | 41 | 38 | 38 | 43 | — | 42 |
| Standard error of the mean | — | — | 10 | 6 | 4 | 5 | 8 | — | 3 |

suffered a remarkably large loss of blood at the parturition, while several patients with relatively low concentrations had very small hemorrhages. The prothrombin content of the blood cannot be a decisive factor for the atonic hemorrhage. When the prothrombin concentrations are not below the values found in normal non-pregnant women, there is no indication for treatment with vitamin K out of consideration to the mother. Whether relatively low prothrombin values may play a role in the development of hemorrhagic diathesis in the infant remains to be studied. No association could be established between the prothrombin concentration and the mother's age, primi- or multiparity, nephropathy or the child's weight.

## Summary.

The prothrombin concentrations in blood at parturition were determined in 253 women. The mean concentration was found 173 ± 2.6 per cent., and the standard deviation was 42 per cent. The means for different groups of patients might indicate a seasonal variation within the year. The material contains no evidence to support the assumption that the prothrombin concentration is of importance with regard to the loss of blood during parturition.

No association could be established between the prothrombin concentration and the mother's age, the number of the birth, nephropathia gravidarum or the weight of the child.

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# Experiments with the Transfer of Infectious Mononucleosis to Monkeys (macacus rhesus) — with Negative Results.

By

JENS BANG.

(Submitted for publication February 20th, 1942).

The problem of the etiology of infectious mononucleosis has not yet been solved. The characteristic blood picture and the specific serological test leave no doubt of its constituting a nosologic entity. What we do know is that it behaves at any rate as an acute infectious disease, and that undoubtedly it leaves permanent immunity. As regards its contagiosity we know that this in any case cannot be great, as it is seldom possible to demonstrate any connection between two cases.

Attempts at finding a specific causative agent have not been lacking; it would, however, be beyond the scope of this article to go into the various hypotheses and the discussion, which is still going on, of the etiological problem. Several microbes have in turn been held responsible, but it applies to the accounts published of positive results of culture that other writers have not been able to repeat the experiments, and that the opinions based upon them cannot be maintained.

The investigations have been supported financially by P. Carl Petersen's Fund.

Nyfeldt claims to have cultivated a microbe from the blood of patients suffering from infectious mononucleosis, belonging to the listerella-group, and after injection into rabbits producing an affection similar to infectious mononucleosis; but numerous others have not succeeded in repeating these experiments. In the Blegdamshospital Stig Thomsen, besides a considerable number of attempts at cultivating a specific microbe from blood and spinal fluid — all with negative results, has carried out a series of experiments with inoculation of the disease on rabbits by means of blood and emulsions of lymph-glands from patients with infectious mononucleosis; these experiments were all negative.

The failure to prove a bacterial etiology has bred a natural tendency to regard infectious mononucleosis as a virus disease, a conception which finds support in other facts, e. g. the neurotropy of the disease and the immunity it leaves. It therefore seemed reasonable to investigate this etiologic hypothesis by trying if it were possible to transfer the disease to the mammal that might beforehand be expected to possess the greatest chance of contracting it, namely the monkey, a task which I undertook at the instigation of the physician-in-chief of the hospital.

Attempts to infect monkeys with infectious mononucleosis have been made twice earlier, in Bruxelles by L. van den Berghe & P. Liessens, in Stockholm by Per J. Wising.

The paper of van den Berghe & Liessens suffers from the defect that it does not appear to me to be proved that the patient supplying the material used for the animal experiments had infectious mononucleosis at all. He was a boy of 4 presenting the picture of angina, swollen cervical lymph-glands and fever, the blood containing 15,000 leukocytes: 16 % monocytes and 22 % lymphocytes (i. e. a total of 38 % mononuclear cells). On the following day 18,000 leukocytes were counted, 8 % of these being monocytes and 21 % lymphocytes (a total of 29 % mononuclear cells), on the 3rd day a similar picture was encountered. No Bunnell test was carried out.

The blood picture described is by no means typical of infectious mononucleosis, if anything it rather seems to disprove this diagnosis. The total number of mononuclear cells is much smaller than one would expect, and as regards the cell count it does indeed show a slight increase in the number of »monocytes» one day, but

no distinction is made between monocytes and the typical infectious mononucleosis cells.

From the patient 4 $cm^3$ oxalated blood is taken and injected into a rhesus monkey. 24 days later the monkey shows leukopenia, namely 3,000 leukocytes as against 15,000 before the experiment, and at the same time the monocytes increase from 2 or 3 % to 21 %. On the following days between 6 and 10 % monocytes are found; the leukocyte count soon returns to normal.

At the height of monocytosis blood is taken and, after bacterial filtration, injected intramuscularly into another monkey, which reacts in a similar way, though with more moderate hæmatological changes; the same thing happens after passage into a third monkey.

In the animals no adenitis or fever was demonstrated. In one of them the Bunnell test was made, but the titer found is below the bottom limit of specificity, and absorption tests are lacking.

The writers believe to have shown that the agent causing infectious mononucleosis is a filtrable virus, a conception, however, which they cannot claim to have proved by these experiments. It is admitted that »something seems to have happened» to the monkeys — the nature of which is difficult to decide; but that the animals should have had infectious mononucleosis is neither proved nor probable. Add to this that, as mentioned above, it seems justified to doubt that the patient, from whom the material for the experiments was taken, had infectious mononucleosis at all.

Of considerably greater interest are the experiments carried out by Wising.

From 3 cases, which, judging by the clinical description, were typical of infectious mononucleosis, an enlarged cervical gland was removed. Microscopy and cultivation showed no presence of bacteria. An emulsion prepared from this gland was injected intracerebrally and subcutaneously into 3 monkeys, 2 cercopitheci and 1 macacus rhesus. In the latter no take occurred, while the 2 cercopithecus monkeys in the course of 18 and 8 days respectively showed universal enlargement of the lymphglands and a rise in the percentage of mononuclears in the blood, which changes could be reproduced in other monkeys (macacus rhesus) by intracerebral and subcutaneous inoculation of an emulsion prepared from lymph-glands from the first monkeys.

During one of the experiments an assistant operator pricked a finger with a knife which had just been used for dividing an extirpated lymph-gland. After 7 days lymphangitis of the arm developed and some days later fever and enlargement of the regional glands in both axillæ and groins, and simultaneously the blood showed a rise in the percentage of mononuclears, and the Bunnell test revealed a temporary increase in titer, maximally 1: 256.

*The objections* that may be raised to the experiments are:

1) It is not sufficiently clear whether the monkeys have been examined more than once before the experiments, so that one does not see the normal variations in the white cell count through some time.

2) While the percentage of mononuclear cells shows a rise during the experiments, this — apart from a single case — does not hold good in any noteworthy degree as regards the *total number* of mononuclears, which most often does not change much, sometimes even decreases.

3) No more differentiated cell count was made to show whether it is only the lymphocyte count that rises, or to what extent abnormal mononuclear cells occur of the type characteristic of infectious mononucleosis in man.

4) Bunnell's test was not made on the monkeys.

As regards the disease of the assistant operator, the blood changes do seem to indicate infectious mononucleosis, though they are not particularly typical. No leukocytosis is present, and at the same time as the percentage of mononuclear cells is high, the total number of leukocytes remains relatively low, so that the total count of mononuclear cells is not very considerably elevated at any time, at most to 5000. The hetero-agglutinin-titer rising to 1: 256 speaks, however, strongly in favour of infectious mononucleosis. Absorption tests have not been carried out, which might have been of additional diagnostic value.

Even if it seems probable that the assistant operator has had infectious mononucleosis, the question remains to be answered whether there exists any causal connection between the disease and the injury he incurred during the experiment, or whether it is a case of mere coincidence.

## The author's experiments.

The problems presenting themselves were:

1) is it possible from patients with infectious mononucleosis to transfer to monkeys a disease similar to human infectious mononucleosis?

2) which are our criteria for deciding the presence of an experimental infectious mononucleosis in the monkey?

3) what is the nature of the pathogenetic agent?

4) which materials from the patients can be used, and which methods of inoculation are effective?

## Which are the materials and methods of inoculation at our disposal?

The following table contains a survey of the experiments carried out, the materials used, and the methods of infecting the animals tried out.

**Table 1.**

| A<br>supposedly contagious materials from patient | B<br>methods of inoculation |
|---|---|
| 1) water used for gargling and passed through filter | inoculation in the rhinopharynx |
| 2) blood, hæmolyzed and passed through filter | intravenous and intramuscular injection |
| 3) blood to which was added heparine | intramuscular injection |
| 4) emulsion prepared from lymph-gland | subcutaneous, intramuscular, intratesticular and intracerebral injection |
| 5) lymph-gland | grafted into the pectoralis muscle |
| 6) rhinitic and sinusitic discharge | inoculation in the rhinopharynx |
| 7) emulsion of tonsil | oral administration |

A) *Concerning materials.*

The patients (numbering 7) were all typical cases of infectious mononucleosis with positive Bunnell test. In all cases the material has been taken at an early stage — during the fever, and the majority of the patients were fairly severely affected.

re 1) The patients gargled and rinsed their mouths and throat with physiologic salt solution. This was passed through a Seiz E. K. filter (incubation tests showed the filtrate to be sterile).

re 2) Blood collected sterilely in tube containing heparin. Adding of equal amount of water to effect hæmolysis. Filtration through Seiz E. K. filter, 20 $cm^3$ were used. (Incubation tests: no bacterial growth).

re 3) Venous blood taken under sterile conditions, to which heparin was added. 20 $cm^3$ were used.

re 4) A swollen inguinal lymph-gland was extirpated under sterile conditions. Microscopy of a small sample showed the changes usually encountered in infectious mononucleosis. The greater part was ground up in a sterile mortar with sand and emulgated in 2 or 3 times the amount of physiologic salt solution. Moderate centrifugalization. The centrifugate was used. (Incubation test: no bacterial growth).

re 5) Swollen inguinal lymph-gland excised and transplanted immediately afterwards.

re 6) From a patient with pronounced rhinitis and sinuitis purulent discharge was obtained by suction and employed without further treatment.

re 7) In a patient whose tonsils were red, swollen, covered with membranes and ulcerations tonsillectomy was immediately performed. The extirpated tonsils was ground up thoroughly and emulgated in equal amounts of water.

It will be seen from this schematic survey that the materials fall into two groups. First, the *sterile* materials used with a view to the hypothesis of a filtrable virus; these materials showed no bacterial growth on the usual media used for cultivation. Second, the *non-sterile* materials used where the experiments *aimed* solely at transferring the disease to the animal, whatever the nature of the causative agent.

B) *Concerning methods of infecting the animals.*

4 monkeys were at the disposal of the author, and 9 experiments were carried out, so that one of the animals was used 3 times, the others 2 times each.

Inoculation in the rhino-pharynx consisted in instillation and rubbing in of the material, in the nose preceded by a superficial scarification of the mucous membrane by means of a pipe cleaner.

The various *injections* (subcutaneous, intramuscular, intravenous, intracerebral, intratesticular) were made in the usual way, under sterile conditions.

*Intracerebral injection.* The monkey was anaesthetized by means of ether. An incision was made through the skin and subcutaneous tissue covering the parietal bone one cm to the left of the sagittal suture. The bone was exposed and the theca pierced by means of a 2 mm dentist's drill as far as the dura. A cannula mounted on a syringe was thrust through the dura and 1 cm into the brain tissue. Here about 4 $cm^3$ of the gland emulsion was deposited. All this under sterile conditions.

## Which are our criteria for deciding the presence of an experimental infectious mononucleosis in the monkey?

It is impossible to know in advance how a monkey will react, if the hypothetic agent takes. It would be convincing if it were possible to produce a disease in all essential respects resembling infectious mononucleosis in man. The following ideal claims would have to be fulfilled:

1) fever and general malaise,
2) adenitis, and, if possible, angina,
3) characteristic changes in the white blood picture,
4) Bunnell test positive, and
5) possibility of further transfer of the disease.

re 1) *The rectal temperature* of the monkeys was between 38 and 39 degrees (Celcius), the highest temperature found before the experiments being 39.5°. In no case fever was present following the experiments, and the *general health* of the monkeys was not affected.

re 2) *Adenitis* that might safely be interpreted as a consequence of specific infection did not occur. Following transplantation of a lymphgland into the pectoralis muscle slight enlargement of regional lymphglands was seen. Angina was not observed.

re 3) The ideal change in the *white blood picture* — analogous to that found in patients with infectious mononucleosis — would be leukocytosis due to an elevation of the number of mononuclear cells, the majority of these being the large »lymphocytes» typical of mononucleosis. In any case a necessity would be so great a change towards relative mononucleosis that the total of mononuclear cells showed a clear increase. Convincing changes of this kind did not occur.

About every 2nd day a leukocyte and differential count was made on the blood of the animals during a period of at least 30 days previous to the experiments to clear up the spontaneous variations and for a minimum period of 30 days following the inoculations.

*Table 2* shows the relations between the total numbers of leukocytes and mononuclear cells per $mm^3$, the lowest and the highest values during the periods preceding and following the inoculations being given.

The *normal white cell count* of the 4 monkeys showed some difference as between the animals and not inconsiderable variations in the individual animal. As to the *differential cell count* sizable variations occurred in the relative distribution. More often than not over half the cells are mononuclear, the rest being polynuclear. The majority of the latter are neutrophile, while one or two per cent are eosinophile. The majority of the mononuclear cells are small lymphocytes; from these there is a gradual transition into large lymphocytes of which an inconsiderable, somewhat varying percentage is encountered. Further, there are one or two per cent of large mononuclears closely resembling the human monocytes. Finally one or two per cent of uncharacteristic mononuclears, transition forms or others difficult to classify, now and then a plasmocyte. As a reliable differentiation between the mononuclear cells is difficult and runs a risk of being subjective, the table shown has only taken into account the total number of white blood cells and the total number of mononuclear cells, as these figures are the essential ones.

Table 2.

| | Leukocytes | | Mono-nuclears | | Bunnell titer | |
|---|---|---|---|---|---|---|
| | min. | max. | min. | max. | min. | max. |
| *Monkey No. 1* before experiment ..... | 8900 | 13500 | 6100 | 9600 | 1:16 | 1:32 |
| *experiment 1:* filtrated rinsewater from mouth inoculated in rhino-pharynx | 8200 | 16100 | 6200 | 11300 | 1:16 | 1:64 |
| *experiment 2:* gland emulsion inoculated intracerebrally ..... | 7200 | 16100 | 3200 | 9200 | 1:16 | 1:16 |
| *experiment 3:* emulgated tonsil orally .. | 10400 | 16500 | 6300 | 10700 | 1:16 | 1:16 |
| *Monkey No. 2* before experiment ..... | 8200 | 13600 | 3700 | 6800 | 1:16 | 1:16 |
| *experiment 1:* gland emulsion subcutaneously and intramuscularly ..... | 8100 | 13700 | 4000 | 6400 | 1:16 | 1:16 |
| *experiment 2:* blood intramuscularly .. | 9400 | 13800 | 4800 | 6200 | 1:16 | 1:16 |
| *Monkey No. 3* before experiment ..... | 11300 | 18100 | 4100 | 9000 | 0 | 0 |
| *experiment 1:* filtrated, hæmolyzed blood intravenously and intramuscularly.. | 11900 | 23400 | 4000 | 8300 | 0 | 0 |
| *experiment 2:* lymph-gland graft ..... | 15500 | 19500 | 6100 | 9400 | 0 | 0 |
| *Monkey No. 4* before experiment ..... | 7100 | 12300 | 3800 | 7500 | 0 | 0 |
| *experiment 1:* unfiltrated rhinitic-sinuitic discharge inoculated in rhino-pharynx ..... | 8000 | 13800 | 4600 | 9100 | 0 | 0 |
| *experiment 2:* lymph-gland implanted and gland emulsion injected intratesticularly ..... | 9000 | 16500 | 3500 | 10000 | 0 | 0 |

During one of the experiments, viz., the 2nd with monkey no. 1, however, certain changes were observed which deserve mention. The monkey was inoculated intracerebrally with lymph gland emulsion on Nov. 13. On the 23rd, 25th and 26th a slight leukopenia was found, namely between 7200 and 8300 cells as against 10000 and 14000 on the days preceding. The cell count during this experiment showed the peculiarity that following the inoculation, from Nov. 16 till Dec. 2, a rise in the number of monocytes was seen, ranging from 7 per cent till 12 per cent as against the normal 2 per cent and 5 per cent.

The phenomenon resembles that encountered by van den Berghe & Liessens. But it cannot be taken as proof that the monkey has been infected with infectious mononucleosis, partly because there was no elevation of the total number of mononuclear cells, partly because adenitis and fever were absent, the general condition of the animal unaffected, and the Bunnell test negative.

Similar phenomena were not found in the other monkeys.

re 4) *Bunnell test.* Of course it would be impossible to know in advance whether a monkey infected with mononucleosis would respond to the Bunnell test. In *Statens Seruminstitut*[1] hetero-agglutinin tests were carried out with sheep blood corpuscles and monkeys' serum in the following dilutions:

1: 8—1: 16—1: 32—1: 64—1: 128—1: 256.

In *man*, with the technique of *Statens Seruminstitut*, a negative response — in adults — weighs heavily against infectious mononucleosis, while a possitive response in the dilution of 1: 256 or even weaker is considered tantamount to infectious mononucleosis. In agglutination tests with the serum dilution 1: 64 absorption is carried out after Davidsohn. By »typical result» is meant that the agglutinin is not absorbed by boiled guineapig kidney, but pronouncedly so by boiled ox blood corpuscles. A reaction of this kind is considered specific of infectious mononucleosis.

Reactions due to serum treatment or unknown reasons are called »atypical».

From the *monkeys* blood was taken for the Bunnell test 2 or 3 times before the experiment and 3 or 4 times during the following 30 days. In table 2 the Bunnell titers are shown.

Serum from 2 of the monkeys showed no agglutination either before or after the inoculation. In the other 2 agglutination was present with low, slightly varying titers both before and after inoculation. In a single experiment agglutination was seen in the serum dilution 1: 64; in this case adsorption tests were carried out showing the reaction to be »atypical».

In no case changes in the titer indicating infectious mononucleosis occurred.

re 5) As there was no response to inoculation, experiments with the passage of the disease were out of the question.

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[1] I am indebted to Dr Martin Kristensen who carried out the Bunnell tests.

## Summary and conclusions:

Experiments with the transfer of infectious mononucleosis to 4 monkeys (macacus rhesus) have been carried out with negative results.

The supposedly contagious *materials*, obtained from 7 patients with infectious mononucleosis, were:

1) *sterile*, namely water used for rinsing the mouth and passed through a bacterial filter, filtrated hæmolyzed blood, unfiltrated blood, lymph gland emulsion or lymph gland. These materials in cultivation tests showed no bacterial growth and were employed with a view to the hypothesis of a filtrable virus,

2) *non-sterile*, namely unfiltrated rhinitic and sinuitic discharges and a tonsil. These were used with the sole object of infecting the animals, whatever the nature of the contagious agent.

*Methods of inoculation* were subcutaneous, intramuscular, intravenous, intratesticular and intracerebral injections, inoculation in the rhinopharynx, oral administration and transplantation.

The monkeys were followed clinically (lymph gland enlargment), as to temperature, leukocyte and differential count besides Bunnell titer. In no case take occurred.

Thus the transfer of infectious mononucleosis to monkeys claimed by other authors has not been confirmed by my experiments. The theory of a *filtrable virus* as the specific agent has found no support, nor is it of course disproved by the fact that the very monkeys used in the experiments proved refractory to inoculation.

The hypotheses of other authors of a *bacterial etiology* were not confirmed, on the contrary. Blood and lymph glands have in no case shown growth of bacteria on the usual media. Nor have non-sterile materials been able to infect the animals.

The etiology of infectious mononucleosis thus remains obscure, and probably the solution of the problem must be approached from other directions. Experiments with human subjects are in progress. The results will be published later.

After the completion of this article a report of *Svenska patologföreningens förhandlingar* in *Nordisk Medicin: 12*, 2916, 1941 has drawn my attention to the fact that Wising in a single case has succeeded in transferring infectious mononucleosis to a human subject.

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Acta Medica Scandinavica. Vol. CXI, fasc. III, 1942.

(From the Department of Hygiene and Bacteriology at the University of Upsala, Sweden (Director: Prof. J. Reenstierna, M. D.).

# Some observations on the morphology of the tubercle micro-organism with special regard to its mycotic nature.

By

EINAR HOLLSTRÖM.

(Submitted for publication January 30th, 1942).

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It is a well known fact that the micro-organism of tuberculosis also occurs in other forms than the classical one, the bacillus of Koch. The possibility of its occurrence in the shape of a real fungus has been much discussed for several decades. Not many firm spots are to be found in this confusion. One of them, a platform for further studies, I wish to emphasize in this short paper, viz. the observations by Reenstierna in 1912 (1): The development in *single* cell cultures of a non-acid-fast fungus of yeast-oidium type, isolated from tuberculous sputum, of acid-fast rods resembling the bacillus of Koch so closely that morphologically and tinctorially they were indistinguishable from it. Reenstierna's observations were confirmed and extended by Gullberg (2) in the years 1933—1935. Furthermore, three papers which appeared in 1941 should be mentioned here: Schaumann (3), Schaumann and Hallberg (4), and Hallberg (5). Finally, it should be recollected that Plá y Armengol (6) saw yeast-like forms in a 53-days-old tubercle bacillus culture. Similar forms seem also to have been observed by Minchin according to Plá y Armengol, who in his paper of 1931 says (in translation

from the German): ». . . they by Reenstierna, by us and by Minchin observed yeast-like forms.»

My own researches carried out chiefly in 1934—1935 deal with a strain of tubercle bacillus (strain 104) which more than twenty years ago was isolated at the State Bacteriological Institute in Stockholm, and has been used there for the preparation of tuberculin. This strain showed, and still shows, the peculiarity described by Reenstierna on pp. 312—313 in his aforesaid paper as follows (in translation from the French): »Each time when a subculture is made from the pellicle (on glycerin bouillon) containing only acid-fast bacilli the bouillon of the new culture begins to grow turbid, generally after two days. About a week later, the bouillon has become entirely clear. It remains so and the piece on the surface develops to a pellicle consisting of acid-fast bacilli. On examination of the bouillon in the stage of turbidity one finds small granulated, diphtheroid rods which are *non-acid-fast* but Gram positive. They are able to grow in a thin layer on glycerin agar, even on fresh common agar». Vide Figs. 1—3, Plate I.

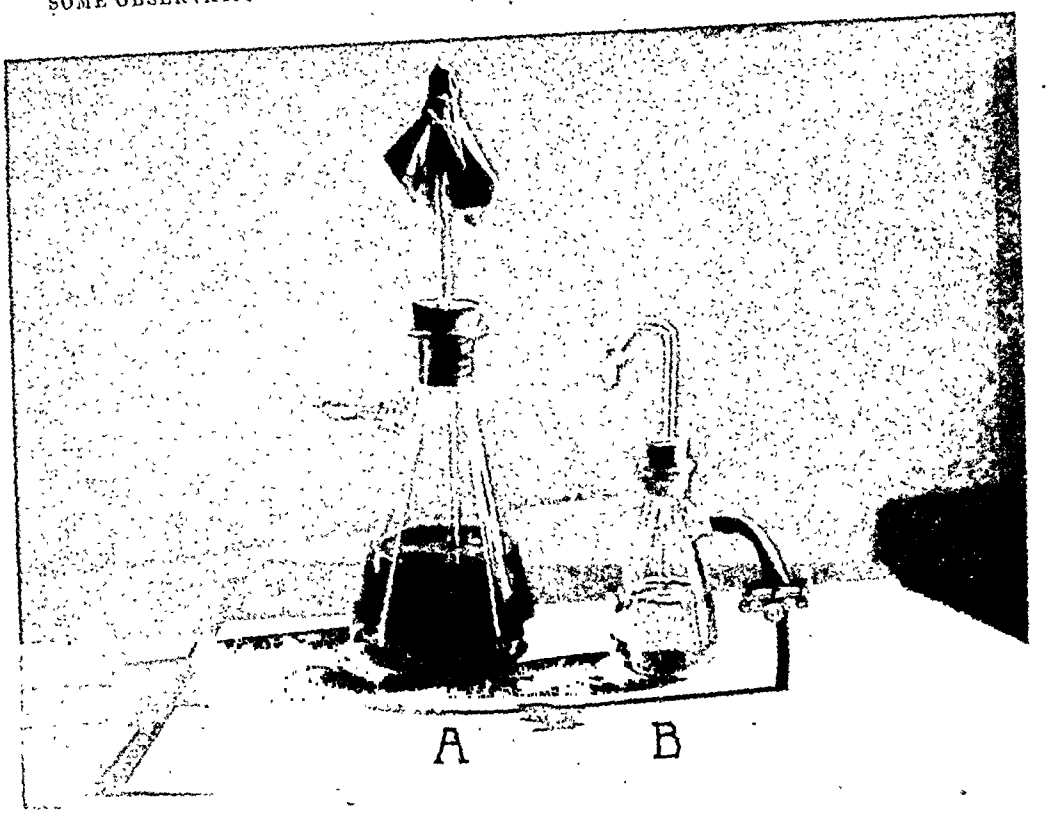
For my studies of the morphological and tinctorial properties of the said diphtheroids daily samples were taken in Oct. and Nov., 1935, during the first 20 days, from a subculture, in a specially fitted flask (Text-fig., A), of strain 104 of the tubercle bacillus. On account of the design of the apparatus the samples used for examination passed directly from the bottom of the flask through a tube, and could therefore not come in contact with the acid-fast bacilli growing on the surface of the medium. From a similar subculture in a flask fitted in another way (Text-fig., B) control samples were obtained. See further explanation of the use of the two apparatus [1].

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[1] Flask A: Size 500 cm³. Its neck is closed by a rubber plug through which passes a tube, which almost reaches the bottom of the flask. The upper end of the tube is closed by a plug of cotton wool, with a paper cap. For pressure equilibrium in the flask there issues from this a lateral pipe with a plug of cotton wool and a paper cap. By pulling out the rubber plug with the tube fitted in it is easy to cultivate on the surface of the substratum. Sampling takes place with a narrow pipette, which is lowered through the perpendicular tube while its upper end is being seared.

Flask B: This is only an ordinary spray-bottle, in which the »blowing-pipe» has been connected to a rubber tube filled with cotton wool as a filtre for the air that is being blown into the flask in order to force out the desired quantity of the culture through the pipe running from the bottom of the flask.

The smears reproduced in figs. 2—9, plate I, have been obtained by the use of flask A. The smears made in the check-test with the use of flask B coincided precisely with those just mentioned.




After 8 days (Pl. I, fig. 4) it was possible in many of the diphtheroids and free from them to establish the presence of acid-fast granules which increased in number during the next four days. On the 12th day there were found in between non-acid-fast and partially acid-fast elements also granulated rods, which showed perfect acid-fastness (Pl. I, fig. 5). After another two days also small, ovoid, acid-fast corpuscles were seen (Pl. I, fig. 6). These correspond to acid-fast, ovoid corpuscles observed by Kedrowski (7), Reenstierna (8) and Walker (9) in leprous material, and by Leczinsky (10) in such of tuberculous origin. On the 20th day there were found in the samples, specially after centrifugation, in addition to all the above described bacterial forms, also sparsely occurring fungus cells of yeast-type, the majority containing acid-fast granules (Pl. I, figs. 7—9).

As all the examinations were carried out under the most stringent conditions of sterility the said fungus cells cannot be considered a contamination. Nor did they ever appear on the surface of the bouillon, nor when cultivating the strain in question on solid media. I therefore find it most probable to consider that some of the

diphtheroid rods growing in the bottom-layer of the medium, poor in oxygen, have developed into fungus forms.

After 10 passages, spreading on agar plates and re-inoculation from one colony, a *single* cell culture of the diphtheroid bacillus strain in its non-acid-fast stage was prepared according to Burri's method. Subcultures of the same were used for animal experiments in order to study the pathogenity of the micro-organism in question and its possible ability of changing into acid-fast forms in the animal body.

During the period July-Sept. 1934, altogether 24 guinea-pigs were inoculated subcutaneously in the right thigh with bacterial emulsion. 10 of the animals received one injection each only of $^1/_7$ slanted agar culture in physiological Na-Cl-solution, while to each of the remaining 14 animals three injections of increasing doses were administered ($^1/_{14}$, $^1/_7$, and $^1/_3$ culture) with intervals of 9 to 15 days. One of the animals (No. 11) belonging to the first group died after about 10 months. At the autopsy *pronounced cachexy* was established and, moreover, in the left lung an abscess the size of a hazelnut, filled with thick, white pus. On microscopical examination this proved first to contain only non-acid-fast diplococci and streptococci, for which reason the abscess was considered a septic one. On closer examination of some films with the use of Hallberg's Nachtblau method for staining tubercle bacilli [1], there were found, besides these cocci, sparsely occuring groups of *acid-fast bacilli of Koch-type* (Pl. II, fig. 1) as well as sporadic acid-fast and non-acid-fast *yeast-like fungus cells* (Pl. II, fig. 2). The anatomo-pathological examination of sections from the lung showed in the neighbourhood of the abscess a purulent pneumonia without tubercles. Some fungus cells were also detected (Pl. II, fig. 3). No macroscopic alterations in the other organs. 9 animals, 2 of the first and 7 of the second group, died between 1 and 10 ½ months after the inoculations had been concluded. No macroscopic changes of the internal organs. However, of the seven animals belonging to the second group, which had all been given three injections, 3 showed a *pronounced cachexy* and 3 a moderate loss of flesh. The three cachectic animals died about 3, 6, and 7 ¼ months after the last injection. 8 animals

[1] Described in his aforesaid paper. Tubercle bacilli take a more or less dark-blue colour.

died intercurrently without any tuberculous alterations, while the remaining 6 were still alive about a year after the injections.

From the majority of the said animals without macroscopic changes of the internal organs pieces of the liver were crushed in physiological Na-Cl-solution and ½ to 2 cm³ of the emulsions injected subcutaneously in the right thigh of new guinea-pigs (in all about 40). One of these animals (No. 49) died after about 4 months. The autopsy revealed a *pronounced cachexy*, and in the left lung *small nodules of typical tuberculous appearance* could be seen. In smears from the same fairly numerous *acid-fast rods of Koch-type* were detected. No macroscopic alterations in other organs. Pieces of the affected lung were crushed in physiological Na-Cl-solution and 1 cm³ of the emulsion injected subcutaneously in the right thigh of each 3 new guinea-pigs which all, unfortunately, died four days later (April 1935). Another piece of the lung was transferred into glycerin bouillon (floating on its surface). A pellicle consisting of acid-fast bacilli developed (Pl. II, fig. 4). Subcultures were made on Petragnani's solid medium. On this medium the bacilli gradually lost their acid-fastness. Thus, in the 5th generation the growth consisted of blue rods with or without red granules as well as of abundantly occurring acid-fast and non-acid-fast granules (Pl. II, fig. 5).

With regard to the pulmonary changes with positive findings of acid-fast bacilli in two of the inoculated guinea-pigs, a spontaneous tuberculous stable infection may possibly have occurred, as this is claimed to have been the case in exceptional instances. But as no such pulmonary infections, containing acid-fast bacilli have ever been established in non-inoculated guinea-pigs of all the various stocks kept in the stables of the Institute of Hygiene and Bacteriology at Upsala [1], I consider it more reasonable to postulate that some of the inoculated non-acid-fast diphtheroid rods have changed into acid-fastness in the bodies of these two animals and in one of them (No. 49) caused typical tuberculous alterations. With regard to guinea-pig No. 11 one might hardly say if the acid-fast rods found played any rôle in producing the abscess in the lung.

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[1] In this connection it should be mentioned that I had myself during the years 1934—1935 — the period when the principal studies on strain 104 were carried out—occasion to perform autopsies on about 50 non-inoculated guinea-pigs, and always with negative findings in the respect here referred to.

Finally, I wish to emphasize that the preceding account is only to be considered as a rendering of *some observations*, that are partially incomplete, and from which no conclusions at all can be drawn.

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## Explanation of Plates I and II.

*Plate 1.*

*Fig. 1.* Smear from a 3-days-old glycerin bouillon culture of strain 104 (in its swarming stage). Stain: Ziehl-Neelsen. Magnification, 1000 diameters. — Reproduction of a picture in Reenstierna's paper in Archives de l'Institut Pasteur de Tunis, 1926, T. XV, fasc. 4.

(Figs. 2—9 show smears prepared at intervals, during Oct.—Nov., 1935, from the bottom-layer of one and the same glycerin bouillon culture of strain 104.)

*Fig. 2.* On the 3rd day. Stain: Ziehl-Neelsen. Magnification, 1000 diameters.

*Fig. 3.* On the 3rd day. Stain: Gram. Magnification, 1000 diameters.

*Fig. 4.* On the 8th day. Sporadic acid-fast granules within and without the rods are seen. Stain: Ziehl-Neelsen. Magnification, 1000 diameters.

*Fig. 5.* On the 12th day. Even entirely acid-fast granulated rods have appeared. Stain: Ziehl-Neelsen. Magnification, 1000 diameters.

*Fig. 6.* On the 14th day. Besides the aforesaid types also ovoid, acid-fast corpuscles occur. Stain: Ziehl-Neelsen. Magnification, 1000 diameters.

*Fig. 7.* On the 20th day. Yeast-like fungus cells containing acid-fast granules have appeared. One of the fungus cells seems to have an orifice where three small acid-fast rods are lying. Stain: Ziehl-Neelsen. Magnification, 1000 diameters.

*Fig. 8.* On the 20th day. Corresponding film stained with methylene blue only. Note. No red granules are seen. Magnification, 1000 diameters.

*Fig. 9.* On the 20th day. Corresponding film stained with Gram. Magnification, 1000 diameters.



Fig. 1.

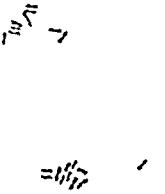


Fig. 2.



Fig. 3.

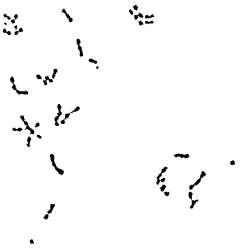


Fig. 4.

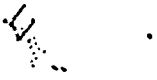


Fig. 5.



Fig. 6.



Fig. 7.



Fig. 8.



Fig. 9.

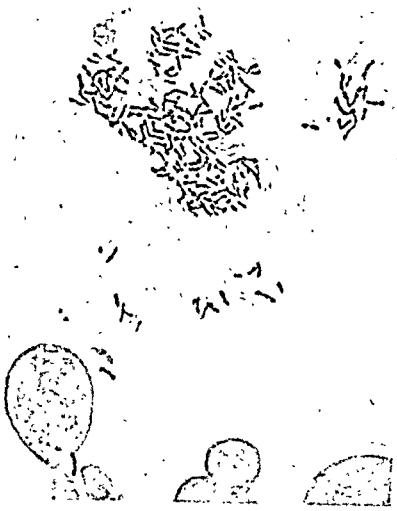


Fig. 1.

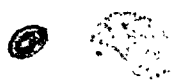


Fig. 2.

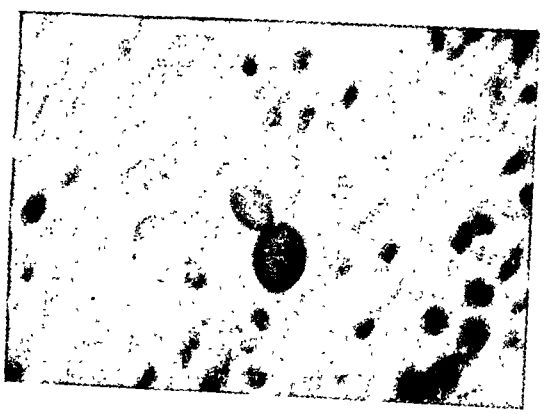


Fig. 3.

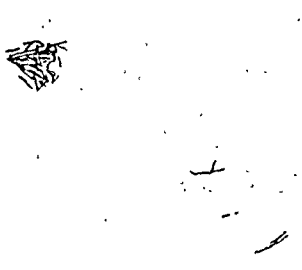


Fig. 4.



Fig. 5.

*Plate II.*

*Fig 1.* Smear from the left lung of a guinea-pig (No. 11). Acid-fast rods of Koch-type. Stain: Hallberg (Nachtblau and neutral-red). Magnification, 1000 diameters.

*Fig. 2.* The same smear. An acid-fast, ovoid fungus cell is seen. Stain: Hallberg (Nachtblau and neutral-red). Magnification, 1000 diameters.

*Fig. 3.* Microphotograph of a section from a piece of the said lung cut from the neighbourhood of an abscess (vide p. 4). Purulent pneumonia. No tubercles. In the centre of the figure are seen two large, ovoid fungus cells. Stain: Haematoxylin — van Gieson. Magnification, 1000 diameters.

*Fig. 4.* Smear from a 7-days-old glycerin bouillon culture originating from a piece of lung with tuberculous lesions from a guinea-pig (No. 49). The smear was taken from the piece of lung which was floating on the surface of the medium. Acid-fast rods resembling Koch's bacilli are seen. Stain: Ziehl-Neelsen. Magnification, 1000 diameters.

*Fig. 5.* Smear from a 32-days-old Petragnani culture (5th generation) originating from the same lung. Visible: Non-acid-fast rods, rods containing acid-fast granules as well as granules, both non-acid-fast and acid-fast, lying in conglomerations or arranged in small chains. Stain: Ziehl-Neelsen. Magnification, 1000 diameters.

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(From the Danish State Department of Health and the Blegdam Hospital, Copenhagen.)

# Chemotherapy in meningococcal meningitis.

By

H. C. A. LASSEN.

(Submitted for publication March 13th, 1942.)

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In no other field, perhaps, has modern chemotherapy achieved such signal and dramatic triumphs as in the treatment of meningitis. Although only a little more than four years have passed since the employment of sulfanilamide and its derivatives was introduced in this field, a great number of works — though mostly based on small materials — have been published already on the therapeutic results, which all show that the prognosis has changed essentially to the better.

There would hardly be any reason here to enter into the literature on this question, a thorough review of which has been given recently by Nissen in a comprehensive work dealing with 31 chemotherapeutically treated cases of purulent meningitis of differing etiology, including 10 cases of meningococcal meningitis.

In the early part of 1941 some aggregate cases of meningococcal meningitis made their appearance almost simultaneously in various parts of the country. In most of these places the number of cases was so small that it would hardly be justified to speak of local epidemics in the proper sense of the term — and only very few of these cases showed any demonstrable epidemiological connection. Outside Copenhagen, a fairly large number of cases (13) were encountered only in the town of Esbjerg, as reported recently by Pedersen & Wilkenschildt.

In the course of the spring and early summer, however, scattered cases of meningococcal meningitis kept being notified to the State Department of Health in a number considerably above the figures for the preceding years. On this account the Health Department decided to collect all the case records of patients treated for meningococcal meningitis in 1941 — to the end of July inclusive — and asked me to work up this material. In this country on the whole, then, the appearance of meningococcal meningitis in 1941 may be said to be of an epidemic character. To this material, comprising 101 patients, I have added 190 cases of meningococcal meningitis admitted to the Blegdam Hospital from 1930 to the latter part of 1941.

## Material.

The composition of the material is evident from Table 1. For practical reasons the material of the Blegdam Hospital is divided into three groups, nearly equal in size.

**Table 1.**

*Survey of Patient Material.*

| | | | |
|---|---|---|---|
| Denmark 1941: | 101 patients | — all the chemotherapeutically treated cases in Denmark outside the Blegdam Hospital (B. H.) in 1941, from January 1 to July 31, inclusive. | |
| B.H. 1940—41: | 54 patients | — all treated with chemotherapy. | |
| B.H. 1935—39: | 65 patients | — 37 treated with chemotherapy, 28 untreated (or treated with serum or vaccine). | 190 |
| B.H. 1930—34: | 71 patients | — all untreated (or treated with serum or vaccine). | |
| Total: 291 patients with meningococcal meningitis. | | | |

The criteria for the diagnosis of meningococcal meningitis are given in Table 2, in which each of these 291 patients with primary purulent meningitis is entered only once: under the heading corresponding to the »best» criterion. In this table the criteria are listed somewhat according to their »rank and precedence».

**Table 2.**

*Principal Criteria of Meningococcal Meningitis in the Individual Cases.*

| | Denmark 1941 | B. H. 1940—41 | B. H. 1935—39 | B. H. 1930—34 | Total |
|---|---|---|---|---|---|
| Meningococci in the blood | 1 | 1 [1] | 0 | 0 | 2 |
| Growth of meningococci in cultures from spinal fluid (most often demonstrated by the State Serum Institute) | 40 | 36 [2] | 44 | 46 | 166 |
| Gram-negative diplococci in the spinal fluid | 54 | 6 | 17 | 17 | 94 |
| Intracellular diplococci in the spinal fluid (methylene blue) | 1 | 0 | 0 | 0 | 1 |
| Growth of meningococci in cultures from the nose and throat | 0 | 0 | 1 | 3 | 4 |
| Meningococcal complement fixation test turning positive after onset of the disease | 2 | 10 | 2 | 4 | 18 |
| Close contact with unquestionable cases of meningococcal meningitis | 1 | 1 | 1 | 0 | 3 |
| Presence of typical petechiæ | 2 | 0 | 0 | 1 | 3 |
| | 101 | 54 | 65 | 71 | 291 |

**Table 3.**

*Distribution of Material According to Sex.*

| | Denmark 1941 | B. H. 1940—41 | B. H. 1935—39 | B. H. 1930—34 | Total |
|---|---|---|---|---|---|
| Men | 63 | 30 | 37 | 44 | 174 |
| Women | 38 | 24 | 28 | 27 | 117 |
| Total | 101 | 54 | 65 | 71 | 291 |
| Died | 22 | 4 | 32 | 46 | 104 |

From Table 3 it will be noticed that the men are in the majority in all the groups of material. So, presumably, it will be justified to conclude that meningococcal meningitis generally attacks men more often than women.

[1] 1 positive out of 28 examined cases.
[2] 36 » » » 48 » »

**Table 4.**

*Age Distribution of the Patients.*

| | Age | | | | | | |
|---|---|---|---|---|---|---|---|
| | <1 | 1—5 | 6—15 | 16—30 | 31—40 | >40 | Total |
| Denmark 1941 ..... | 18 | 32 | 20 | 18 | 6 | 7 | 101 |
| B. H. 1940—41 ..... | 8 | 16 | 10 | 14 | 4 | 2 | 54 |
| B. H. 1935—39 ..... | 34 | 24 | 2 | 3 | 0 | 2 | 65 |
| B. H. 1930—34 ..... | 26 | 31 | 7 | 5 | 2 | 0 | 71 |
| Total | 86 | 103 | 39 | 40 | 12 | 11 | 291 |

According to Table 4, meningococcal meningitis occurs mostly in the age classes under 6 years. It will further be noticed that the younger groups (1940—1941) in this material do not show the same distribution as the two older groups (1930—1939). Undoubtedly this is associated with the well-known fact that the age distribution of epidemic diseases changes when the disease, from being endemic, goes on to become epidemic.

**Table 5.**

*Age Distribution of Patients in an »Epidemic« and an »Endemic« Material of Meningococcal Meningitis.*

| | Age | | | | | | |
|---|---|---|---|---|---|---|---|
| | <1 | 1—5 | 6—15 | 16—30 | 31—40 | >40 | Total |
| Epidemic, 1941..... | 24 | 46 | 29 | 28 | 10 | 8 | 145 |
| Endemic, 1930—40 .... | 62 | 57 | 10 | 12 | 2 | 3 | 146 |

Table 5 gives the age distribution for all the cases in 1941 when the disease was of an epidemic character, as compared to the age distribution of the Blegdam Hospital from 1930 to 1940, during which period the disease did not occur epidemically in Copenhagen.

This table shows plainly that meningococcal meningitis under endemic conditions is preponderantly a disease of infants and young children, whereas under epidemic conditions it is widely distributed over all age classes up to 30 years. As will be pointed out later on, this fact is rather important because the prognosis

of meningococcal meningitis is far more serious in the younger age classes — especially in children under one year — than in the older.

Table 6 shows the distribution of the cases over the 12 months of the year. Here, too, the epidemic cases of 1941 are tabulated in relation to the endemic cases, which are divided into two groups in order to see more readily whether meningococcal meningitis may show any characteristic seasonal distribution when it occurs endemically.

**Table 6.**

*Seasonal Distribution of the Patients in an »Epidemic« Material as Compared to 2 Groups of »Endemic« Cases.*

| | Month | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | Total |
| Epidemic, 1941 ..... | 3 | 9 | 22 | 33 | 30 | 15 | 10 | 10 | 11 | 3 | 6 | 3 | 145 |
| Endemic, B. H. 1935—40 | 6 | 9 | 11 | 5 | 12 | 4 | 4 | 7 | 5 | 3 | 3 | 6 | 75 |
| Endemic, B. H. 1930—34 | 3 | 8 | 4 | 6 | 15 | 9 | 3 | 5 | 4 | 4 | 5 | 5 | 71 |
| | | | | | | | | | | | | | 291 |

It will be noticed that the »epidemic« cases in 1941 are distributed rather evenly round March and April, which represent the maximum. As the collection of the present material stopped at the end of July, this table can tell us nothing about the distribution after July 1941. Also the endemic cases show some accumulation round the month of April, but the figures are too small to allow of any definite conclusions.

## Treatment.

Table 7 gives a survey of the character of the treatment and the number of deaths in the various therapeutic groups. These groups are designated after the therapy employed as the only, or principal treatment in the given cases. The greater majority of the cases within the various groups have been »clear-cut« therapeutically, but each of the groups treated chemotherapeutically includes a few cases in which more than one remedy was employed. There was only a couple of these cases in the material of the Blegdam

**Table 7.**

*Deaths in Relation to the Nature of the Treatment.*

| | B. H. 1930—34 | | B. H. 1935—39 | | B. H. 1940—41 | | Denmark 1941 | | Entire material | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Deaths | Total | Deaths | Total | Deaths | Total | Deaths | Total | Deaths |
| No treatment whatever | 10 | 8 | 10 | 5 | | | | | 20 | 13 |
| Vaccine treatment alone | 22 | 13 | 17 | 13 | | | | | 39 | 26 |
| Antimeningococcus serum or serum + vaccine | 34 | 21 | 1 | 1 | | | | | 35 | 22 |
| Inj. of acridin derv., in some cases + vaccine | 5 | 4 | | | | | | | 5 | 4 |
| Total No. of untreated | 71 | 46 | 28 | 19 | | | | | 99 | 65 (3) |
| Sulfanilamide, alone per os or intramuscularly | | | 7 | 1 | | | 10 | 4 | 17 | 5 |
| Sulfanilamide per os or i. m. + intraspinally | | | 24 | 9 | | | 4 | 3 | 28 | 12 |
| Total treated w. sulfanilamide | | | 31 | 10 | | | 14 | 7 | 45 | 17 (2) |
| Acetylsulfapyridine per os | | | | | 3 | 0 | | | 3 | 0 |
| Acetylsulfapyridine per os + sulfanilamide intraspinally | | | 5 | 2 | | | | | 5 | 2 (2) |
| Sulfapyridine per os + sometimes i. m. or i. v. | | | | | 9 | 1 | 19 | 3 | 28 | 4 |
| Sulfapyridine per os + intraspin. | | | | | | | 1 | 0 | 1 | 0 |
| Sulfapyridine per os + sulfapyridine intraspinally | | | 1 | 1 | | | 7 | 3 | 8 | 4 |
| Total treated with sulfapyridine | | | 1 | 1 | 9 | 1 | 27 | 6 | 37 | 8 (2) |
| Sulfathiazole alone per os | | | | | 38 | 3 | 31 | 4 | 69 | 7 |
| Sulfathiazole per os + i. m. or i. v. | | | | | 3 | 0 | 14 | 2 | 17 | 2 |
| Sulfathiazole per os + other chemotherapeutics intraspin. | | | | | | | 5 | 2 | 5 | 2 |
| Total treated with sulfathiazole | | | | | 41 | 3 | 50 | 8 | 91 | 11 (8) |
| Sulfamethylthiazole | | | | | | | 6 | 1 | 6 | 1 |
| Various chemotherapeutics simultaneously per os | | | | | 1 | 0 | 4 | 0 | 5 | 0 |
| Total | 71 | 46 | 65 | 32 | 54 | 4 | 101 | 22 | 291 | 104 |

The figures in brackets to the right of some of the figures in the last column give the number of patients who died within 24 hours after admission.

Hospital, but a few more in the material collected by the State Department of Health in 1941.

Table 8 gives the lethality observed under the various forms of treatment, based on the figures in Table 7. The gross lethality is calculated per total number of deaths in the respective groups; the reduced lethality is the number for the gross lethality minus the cases in which the patient died within 24 hours after the commencement of the treatment or, in the untreated cases, within 24 hours after admission to the hospital.

**Table 8.**

*Gross Lethality and Reduced Lethality in Relation to the Nature of the Treatment.*

| | No. of patients | Gross lethality % | Reduced lethality % |
|---|---|---|---|
| Untreated patients ..... | 99 | 66 | 65 |
| Treated with sulfanilamide..... | 45 | 38 | 35 |
| » » sulfapyridine..... | 37 | 22 | 17 |
| » » sulfathiazole ..... | 91 | 12 | 4 |

Table 8 illustrates strikingly how extraordinarily the prognosis of meningococcal meningitis has improved since the introduction of sulfanilamide and its derivatives in the therapy. As mentioned before, however, it is necessary to subdivide the therapeutic groups into age classes, in order to arrive at a fair estimation of the effectivity of the various remedies.

Perhaps it is not superfluous to add, that I do not from these results consider it proved, that sulfathiazole is more efficacious than sulfapyridine in the treatment of meningococcal meningitis — but it is at least equally good and sulfathiazole medication is accompanied by fewer complications than treatment with sulfapyridine.

Although the dosage of the three sulfonamides mentioned in tables 7 and 8 cannot be compared directly it is evident from the case records that in nearly all cases large doses have been employed irrespective of the drug used.

From Table 9 it will be noticed that only a few age groups are really comparable and that only a few conclusions may be drawn

**Table 9.**

*Gross Lethality and Reduced Lethality in Relation to the Age of the Patients and Nature of the Treatment.*

| | | Age | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <1 | 1—5 | 6—15 | 16—30 | 30—40 | >40 | Total |
| Untreated patients | No. of patients | 39 | 43 | 9 | 5 | 2 | 1 | 99 |
| | Gross lethality | 80 % | 63 % | (3) | (2) | (2) | (0) | |
| | Reduced » | 79 % | 60 % | (0) | (0) | (0) | (0) | |
| Sulfanilamide | No. of patients | 21 | 18 | 1 | 5 | 0 | 0 | 45 |
| | Gross lethality | 38 % | 33 % | (1) | (2) | | | |
| | Reduced » | 35 % | 33 % | (0) | (1) | | | |
| Sulfapyridine | No. of patients | 3 | 14 | 8 | 6 | 3 | 3 | 37 |
| | Gross lethality | (1) | 21 % | (2) | (1) | (0) | (1) | |
| | Reduced » | (0) | 15 % | (1) | (0) | (0) | (0) | |
| Sulfathiazole | No. of patients | 15 | 26 | 19 | 20 | 6 | 5 | 91 |
| | Gross lethality | 47 % | 8 % | 0 % | 5 % | (0) | (1) | |
| | Reduced » | 20 % | 0 % | 0 % | 5 % | (0) | (1) | |

as to the relative effectivity of the various chemotherapeutics on the basis of this material which otherwise may be said to be even fairly large. The figures in brackets in the groups comprising less than 10 patients give the number of patients who died in the respective therapeutic age group (recorded under the heading »gross lethality») and the number of patients in the groups who died in less than 24 hours after the institution of treatment or — this applies to the untreated cases — who died within 24 hours of their admission to the hospital (recorded under the heading »reduced lethality»).

The only conclusions that may be drawn with a fair degree of certainty from the figures recorded in Table 9 are the following:

1) In the age class of 1—5 years, sulfathiazole has improved the prognosis enormously, sulfapyridine essentially, and sulfanilamide probably in some degree.

2) In the age class under 1 year we have only the sulfanilamide and sulfathiazole groups for comparison with the untreated. Both these remedies have improved the prognosis in some degree,

but the obvious superiority of sulfathiazole in comparison to sulfanilamide in the age class of 1—5 years is here considerably less pronounced — if it be present at all.

As pointed out below, the generally poor prognosis for the age class under 1 year is undoubtedly due in part to the fact that the clinical features of the disease in this age class often are rather uncharacteristic so that a good many of these children were not given the proper treatment until very late in the course of their affection.

3) In the age classes over 6 years we have no available material for comparison with the sulfathiazole results. These results are strikingly excellent — only 2 out of 50 patients died, and one of these within 24 hours of the institution of the treatment — and it is not very likely that sulfanilamide or sulfapyridine would have given just as good results, let alone any better.

Looking into what day of illness the chemotherapy was commenced, we get the information recorded in Table 10.

**Table 10.**

*Chemotherapy Instituted on Day of Illness.*

| Day of Illness | 1 | 2 | 3 | 4 | 5 | 6—10 | >10 | ? | Total No. of patients |
|---|---|---|---|---|---|---|---|---|---|
| Denmark, 1941 .... | 8 | 38 | 19 | 13 | 5 | 7 | 10 | 1 | 101 |
| B. H. 1937—41 .... | 4 | 21 | 14 | 14 | 12 | 15 | 9 | 2 | 91 |
| Total ..... | 12 | 59 | 33 | 27 | 17 | 22 | 19 | 3 | 192 |
| Died..... | 0 | 20 | 2 | 6 | 2 | 4 | 3 | 2 | 39 |

As will be noticed, in a greater majority of the cases the chemotherapy was instituted early in the disease. This applies to the fatal cases, too, in half of which the treatment was commenced before the third day of illness; and in three-fourths of these cases it was instituted before the sixth day of illness. Considering the patients who were hospitalized late (10' day of illness or later). they were nearly all infants or children in the first three years of life.

The material is further tabulated with a view to the degree of their affection in the individual cases, in order to see whether this was about the same in the three large groups treated with

chemotherapeutics and in the untreated group. Here the condition of the patients on admission to the hospital is taken as the basis for comparison, the patients being divided after the data given in the case records — as far as practicable — into two classes, according to the degree in which they were affected (Table 11).

As will be noticed, there is no particular difference in this respect between the groups — they are fully comparable.

A fair idea about the effectivity of the new chemotherapeutics in general and their relative effectivity is gained when we look into how many days it takes after the institution of treatment

**Table 11.**

*Degree of Affection of the Patients on Admission to the Hospital.*

| | No. of patients | Greatly exhausted or exhausted | Affected but not exhausted | No information |
|---|---|---|---|---|
| Sulfanilamide .... | 45 | 55 % | 42 % | 1 patient |
| Sulfapyridine..... | 37 | 76 % | 21 % | 1 » |
| Sulfathiazole ..... | 91 | 64 % | 36 % | 0 » |
| Untreated ..... | 99 | 70 % | 30 % | 0 » |

before the temperature is lowered permanently to a level below 38°. This information is given in Table 12. For the untreated cases a record is made of the number of days that pass after the admission before the temperature kept constantly under 38°. Only patients who survived the disease are included in this tabulation.

**Table 12.**

*Temperature permanently under 38° in Relation to the Duration of the Treatment.*

Discharged Patients.

| | Days | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0[1] | 1 | 2 | 3 | 4 | 5—10 | 11—15 | >15 | ? | Total |
| Sulfanilamide .. | | | 3 | 2 | 1 | 14 | 5 | 3 | | 28 |
| Sulfapyridine .. | 6 | 7 | 6 | 1 | 3 | 3 | 2 | | 1 | 29 |
| Sulfathiazole .. | 5 | 24 | 12 | 3 | 3 | 28[2] | 3 | | 2 | 80 |
| Untreated..... | 2 | | 1 | | | 5 | 5 | 21 | | 31 |

[1] The patients in this column showed at no time a temperature over 38°.
[2] No doubt, this group includes several patients with drug fever.

In the untreated group, as will be noticed, it is only in exceptional cases that the temperature fell permanently below 38° within 4 days, whereas 60 % of the patients in this group kept having a temperature over 38° for more than 15 days — often much longer. Also on treatment with sulfanilamide it happens but seldom that the temperature falls off within 4 days — in two-thirds of the cases it took 5—15 days before this fall set in. Under sulfapyridine and sulfathiazole treatment it is quite a *different matter*: in a greater majority of the cases the temperature falls permanently below 38° within the first four days of treatment — this applies especially to sulfapyridine.

As to the point of time for the disappearance of the meningococci from the spinal fluid under the various forms of chemotherapy, the case records give but very scanty information. In the rather few cases where it has been possible to establish this point with a fair degree of accuracy, it is found most often to take a couple of days before the spinal fluid becomes sterile. In one case, however, the presence of meningococci could still be demonstrated after 16 days of treatment.

Also the duration of the stay in the hospital after the institution of chemotherapy may serve to throw some light on the effectivity of the treatment. An account of this feature is given in Table 13. In nearly all the cases the chemotherapeutic treatment was instituted on the day of admission; in a few cases, however, this treatment was not commenced till some days after admission, but this is taken into account in the tabulation. For the untreated patients the duration of the stay in the hospital is recorded.

**Table 13.**

*Duration of Hospitalization for Discharged Patients.*

| | Days | | | | | | |
|---|---|---|---|---|---|---|---|
| | ≦20 | 21—30 | 31—40 | 41—50 | 51—60 | >60 | Total |
| Sulfanilamide ..... | 1 | 5 | 6 | 7 | 2 | 7 | 28 |
| Sulfapyridine ..... | 6 | 11 | 6 | 4 | 1 | 1 | 29 |
| Sulfathiazole ..... | 13 | 34 | 22 | 7 | 3 | 1 | 80 |
| Untreated ..... | 0 | 2 | 3 | 5 | 4 | 20 | 34 |

Table 13 shows that the untreated patients are hospitalized considerably longer than the ones given chemotherapy, and that

sulfapyridine and sulfathiazole treatment shortens the stay in the hospital considerably more than sulfanilamide therapy.

It is the general impression that defects in these patients after recovery are relatively rare after chemotherapy. Hitherto, as far as I know, no comparative report with a view to this feature has yet been published on any fairly large material which includes also untreated patients. Therefore, the frequency and character of the defects in the discharged patients were looked into — and this account covers all the patients discharged (Table 14). Unfortunately, the number of discharged untreated patients is considerably smaller than the number of discharged patients treated with chemotherapy.

**Table 14.**

*Defects in Discharged Patients.*

| Discharged | Total | Discharged with defect | Discharged with serious defect | Serious defect, in percentage |
|---|---|---|---|---|
| After chemotherapy | 153 | 14 | 4 | ca. 3 % |
| Untreated ..... | 34 | 7 | 4 | ca. 12 % |

From Table 14 it appears as if the frequency of defects, both serious and less serious, is smaller among discharged patients treated with chemotherapy than among discharged untreated patients. The character of the defects is the same in all the groups: strabismus, facialis paresis, impairment of the hearing, impairment of the vision or blindness, hydrocephalus. The defects reckoned as serious are: marked impairment of the hearing or vision, hydrocephalus.

In this material, toxic manifestations in connection with chemotherapy have generally been few and of minor importance: Medicamental rash has been recorded in the cases of 8 patients, drug fever in 6, hematuria in 5, fairly severe anemia in 6. There was no instance of clinical arganulocytosis. Considering that nearly all of these patients were given large doses of the chemotherapeutics and often for a rather considerable length of time, the frequency of these toxic manifestations is really very low.

In conclusion, particular mention is to be made of the dosage of sulfathiazole in the treatment of meningococcal meningitis.

In the Blegdam Hospital, for the present, sulfathiazole has been preferred to all other sulfanilamide derivatives in the treatment of meningococcal meningitis — for various reasons. Sulfathiazole is at least just as effective as any of the tried-out chemotherapeutics advanced so far — presumably even more effective. At any rate, it gives less inconvenience than its closest competitor — sulfapyridine. With sulfathiazole the treatment can be carried through nearly always with oral administration of the remedy alone (in 38 out of 41 patients treated in the Blegdam Hospital in 1941); and in the total material presented here it has given considerably better results than were obtained with oral + intraspinal

**Table 15.**

*Schema of Dosage for Oral Sulfathiazole Medication in Meningococcal Meningitis.*

(Doses given in the Blegdam Hospital in 1941.)

| Age (years) | Initial dose | Total in age class |
|---|---|---|
| <1 | 0.25 g. + 0.25 g. 3 h. later + 0.125 g. every 3 hours.<br>1 g. + 1 g. 4 hours later + 0.50 g. every 4 hours. | ca. 15 g. |
| 1—<3 | 1 g. + 0.50 g. 4 hours later + 0.50 g. every 4 hours.<br>1.50 g. + 1.50 g. 4 hours later + 1 g. every 4 hours. | 11—29 g. |
| 3—<6 | 1.50 g. + 1 g. 4 hours later + 1 g. every 4 hours.<br>1.50 g. + 1.50 g. 4 hours later + 0.75 g. every 4 hours.<br>2 g. + 2 g. 3 hours later + 1 g. every 3 hours. | 25—51 g. |
| 6—<10 | 1.50 g. + 1.50 g. 4 hours later + 1 g. every 4 hours.<br>2 g. + 2 g. 4 hours later + 1 g. every 4 hours. | 28—47 g. |
| 10—<15 | 1.50 g. + 1.50 g. 4 hours later + 1 g. every 4 hours.<br>2 g. + 2 g. 4 hours later + 1 g. every 4 hours. | 28—45 g. |
| 15—<20 | 2 g. + 2 g. 3 hours later + 1.50 g. every 3 hours. | 56 g. |
| ≧20 | 1 g. every 4 hours.<br>2 g. + 2 g. 3 hours later + 1 g. every 3 hours.<br>2 g. + 2 g. 3 hours later + 2 g. 3 hours later + 1.50 g. every 3 hours. | 30—74 g. |

therapy. In our opinion, therefore, intraspinal chemotherapy has to be given up unconditionally. In passing, it may be mentioned that, according to our experiences, the daily lumbar puncture is of no benefit to the treatment in general.

We have individualized the sulfathiazole treatment considerably after the age of the patients and the severity of the disease — not only the initial dose but also the subsequent dosage and the duration of treatment. In several cases the concentration of the drug in the blood and in the spinal fluid has been determined. These features will not be discussed here, however, as they will form a part of a more comprehensive work to be published in the near future, dealing with the passage of sulfathiazole from the blood stream to the cerebrospinal fluid in various forms of meningitis. As shown first by Roelsen, sulfathiazole passes more readily from the blood to the spinal fluid in patients with purulent meningitis than in patients with serous meningitis or in normal persons.

On an average, our patients have received sulfathiazole for 5—10 days, which in most cases means that the medication is continued for 3—5 days after the fall of the temperature. This may possibly be rather long — a little shorter duration of treatment might perhaps suffice — but as the inconveniences from the treatment have been so slight and the results so excellent, we think it is perfectly safe to recommend the dosage outlined in Table 15. This dosage was employed in the treatment of the 41 patients with meningococcal meningitis admitted to the Blegdam Hospital in the first ten months of 1941. Of these 41 patients 38 were given sulfathiazole by mouth exclusively; altogether 3 patients died, 2 of them within 24 hours after the institution of treatment.

In cases requiring parenteral administration of sulfathiazole we have given doses corresponding nearly to the abovementioned, but in this way: each tablet (50 cg.) is replaced by one ampulla of sulfathiazole (40 cg.).

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# The occurrence of alcoholics and their treatment.

## A social-statistical analysis for the town of Malmö 1929—1938.

By

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(Submitted for publication December 22nd 1941).

## Introduction.

Sweden, better than other countries, affords possibilities of obtaining an orientation regarding alcoholics from a social point of view. According to a law, in force from July 1st 1916, official organizations, i. e. temperance boards, were formed for the purpose of taking care of inebriates. Alcoholism in Stockholm has earlier been the subject of a more detailed analysis (Dahlberg-Stenberg 1934, and Dahlberg 1939). The present investigation intends to offer a survey of the conditions prevailing in Malmö. The author wishes to express his warm thanks for the courtesy and great interest evinced by the Temperance Board of the town of Malmö.

On the whole, the present inquiry has been performed in conformity to a plan used in the earlier investigations. Above all, the experiences gained in those investigations have availed insomuch that, now, it has been possible to concentrate on the principal points of the subject. The former studies had to be pursued on a larger scale, as it was impossible to know, then, which data would be of use and offer important results. In regard to methods the reader is referred to my papers mentioned above. In the present investigation only a brief survey will be given. As to the methodical problems, they will only be accounted for to the extent necessary for the comprehension of the work.

## The character of the material.

The cases refer to the period 1929—38. It was considered appropriate to cease the investigation at the first year of war when circumstances could no longer be regarded as what is usually termed normal. The material comprises 1.313 alcoholics and a small number of persons who had been reported, but were not alcoholics in the sense of the law. With respect to the last-mentioned group, consisting of 35 persons within a period of 10 years, it may be noted that reports have, doubtless, been justified in several of these cases. The authorities brought charges against 16 persons and private individuals reported 19 cases. Intervention by the authorities (i. e. the Police, the Poor Relief, etc.), has certainly not been carried into effect without grounds. Also, reports by private persons (i. e. relatives, etc.), have, no doubt, in several cases, been sufficiently well founded to warrant a close examination. Still, it has not been possible to determine the extent to which altogether unjustified charges have occurred. However, 6 of those reported had been convicted for drunkenness twice, at the least, and 2 cases had been convicted 4 times for the same reason. Actually, these data are of interest, illustrating as they do the wellknown fact that the Temperance Board does not interfere unnecessarily. A careful inquiry is always made to ascertain whether the report was justified. If this were not so, a strong reaction would very soon manifest itself. The press in Sweden, as in many other countries, has, up to the present war, been exceedingly vigilant concerning infringement upon individual freedom even with regard to the liberty to consume alcohol. In actual fact, it is never said in the Swedish press that the Temperance Board has intervened without a cause. This is, consequently, a good guarantee that those taken care of by the Temperance Board are real alcoholics.

In this connection, it may be pointed out that a person is considered to be an inebriate in the sense of the law when he is intoxicated almost daily, involving also incapability on his part to execute his social duties. It is important to distinguish between alcoholism in a medical sense and in a social sense. In the former case, the individual discloses symptoms of disease which remain even after the dose of alcohol has been subjected to oxidation or excre-

the analysis of the Stockholm material disclosed many individuals who were inebriates and fit for detention long before they were reported. It is probable that analogous conditions prevail in Malmö, that is to say, to a certain extent, people die or have time to move to another place, where the Temperance Board is less active than in the cities, before a charge is brought against them. Also in this connection the figures stated are minimum ones.

**Table 1.**

Number of men and of women reported to the Temperance Board of Malmö. (Persons not detained are excluded).

| Year | Men | | | Women | | | Total |
|---|---|---|---|---|---|---|---|
| | Registered in Malmö | Not registered in Malmö | Total | Registered in Malmö | Not registered in Malmö | Total | |
| 1929 | 55 | — | 55 | 1 | — | 1 | 56 |
| 1930 | 82 | — | 82 | 3 | — | 3 | 85 |
| 1931 | 97 | — | 97 | 2 | — | 2 | 99 |
| 1932 | 96 | — | 96 | 3 | — | 3 | 99 |
| 1933 | 132 | 9 | 141 | 11 | 1 | 12 | 153 |
| 1934 | 104 | 5 | 109 | 3 | 1 | 4 | 113 |
| 1935 | 117 | 9 | 126 | 6 | — | 6 | 132 |
| 1936 | 144 | 13 | 157 | 11 | — | 11 | 168 |
| 1937 | 164 | 23 | 187 | 7 | — | 7 | 194 |
| 1938 | 176 | 26 | 202 | 12 | — | 12 | 214 |
| 1929—38 | 1167 | 85 | 1252 | 59 | 2 | 61 | 1313 |

The distribution of the material is shown in Table 1. The number of reported cases has increased up to the present time, owing, in some degree, to the growth of the population.[1] However, in the first place, this increase may be suspected of being due to better competency on the part of the Temperance Board. The staff employed has grown in number up to the present time, a fact which may have produced this greater efficiency. But, on the other hand, it may be an indication of the necessity to add to the staff when the number of inebriates increases. Before 1933, the duties of the

[1] 254 cases were reported for the first time in the year 1939. In 1940, 359 new cases were reported (those not considered as addicted to alcoholism are not included).

Temperance Board were performed by the Poor Relief Board. At the commencement of the year 1933, a special Temperance Board was established. Probably, this serves to explain the increase in number of the individuals reported in 1933, as compared to the preceding and the following years. However, if the increased number of reported cases is due to the greater efficiency on the part of the Temperance Board, it is to be expected that a proportionally greater number of individuals reported by the authorities should be obtained. It is hardly possible for the Board directly to stimulate private persons to report. Nevertheless, no extensive deviation seems to have taken place. It is found that the authorities' share in the reports has, if anything, diminished while statements by private persons have increased. During the period 1929—33, 35.5 % were reported by private individuals; in the period 1934—38 the corresponding figure was 41.5 %. Under the circumstances, it is difficult to reach definite conclusions. The intensified reporting frequency may be the sign of a deterioration of temperance conditions. But the reason may, as well, be that the public has become increasingly conscious of being able to apply to the Temperance Board. The degree to which the activity of the Temperance Board, which must always be based on cooperation between private individuals and the authorities, has achieved absolute efficiency eludes estimation. However, as will be seen from figures which will be discussed later on, there is reason to believe that the cases of alcoholism reported during the earlier period were, on an average, of a more serious nature than those of the later period. That is to say, it was more often considered necessary to adopt vigorous measures, e. g., internment, in the former period.

With respect to reporting authorities, it may be mentioned that the Poor Relief has reported a very small number of cases, viz., 4.2 %. Cases reported by a doctor or a hospital constitute only 0.5 %. This is remarkable, as there is occasion to suppose that the Poor Relief, as well as doctors, to an exceptionally great extent come into contact with inebriates. Drunkards are compelled to apply to doctors and to hospitals because of ill-health of various kinds. They have to turn to the Poor Relief owing to bad circumstances. However, requests for assistance are, apparently, delivered in such a manner that the character of the individual seldom is noticed.

Finally, concerning the character of the material, it may be stated that 87 inebriates, reported to the Temperance Board, have been excluded in the following analysis because they were not registered in Malmö. They comprise 6.6 % of the total number of those reported. On the other hand, alcoholics registered in Malmö, who had been reported to another temperance board in another part of the country and, there, subjected to intervention, are not included in the material. This circumstance and the fact that well-to-do inebriates are reported to a small extent, as already mentioned, tends to give too low figures for calculations of risk. Lastly, it may be pointed out that women only comprise 4.6 % of the total material.

## The risk of alcoholism in Malmö.

In the fore-mentioned earlier investigations the risk of alcoholism in Stockholm, as regards men, was seen to amount to about 10 % (during the years 1926—35). This signifies that a tenth of the men living to an age of 70 years are reported at least once to the Temperance Board and are regarded as alcohol addicts.

In this connection, it may be observed that a calculation of how great a part of the Stockholm population annually is reported and taken care of on account of alcoholism will not form a true estimate of conditions. The figure obtained is approximately one in a thousand. In order to arrive at this figure, the number of those reported in the whole population of men, women and children is computed. The children cannot become inebriates and the women do so comparatively seldom. Therefore, the women and children should not be employed for the purpose of attaining low percentage figures for the men. A differentiation between the sexes and between individuals of different ages should be made. In reality, the risk run by young individuals is inconsiderable. A person can only be designated an alcoholic after abuse of spirits of many years' standing. In Stockholm the risk culminates at about the age of 45, thereafter decreasing.

If a true orientation of conditions is desired, risk figures should be calculated in order to acquire a conception of the number of 20-year-olds, 25-year-olds, 30-year-olds, etc., who are taken care of annually for the first time. Then, one person is imagined to live through these ages, respectively and is exposed to the risks involved,

in their proper turns. In this way, by summing up the risks, a cumulative figure is obtained for the total risk, during the course of life, of being reported at least once on account of alcoholism. The same method of calculation has been employed with regard to the men in Malmö. The result is set forth in Table 2 and Fig. 1 and 2.

**Table 2.**

The risk of alcoholism in the population of Malmö.

| Age at first detention | Men 1929—33 | | | | Men 1934—38 | | | | Women 1929—38 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Average population | Cases of alcoholism | ‰ | Cumulative number in 1000 individuals | Average population | Cases of alcoholism | ‰ | Cumulative number in 1000 individuals | Average population | Cases of alcoholism | ‰ | Cumulative number in 1000 individuals |
| 15—19 | 5237 | 7 | 1.3 | 1.3 | 5618 | 48 | 8.5 | 8.5 | 6248 | 1 | 0.16 | 0.08 |
| 20—24 | 5844 | 33 | 5.6 | 6.9 | 6246 | 67 | 10.7 | 19.1 | 7678 | 6 | 0.78 | 0.47 |
| 25—29 | 5443 | 43 | 7.9 | 14.9 | 6913 | 69 | 10.0 | 28.9 | 7418 | 7 | 0.94 | 0.94 |
| 30—34 | 4973 | 60 | 12.1 | 26.8 | 6140 | 82 | 13.4 | 41.9 | 6443 | 13 | 2.02 | 1.95 |
| 35—39 | 4329 | 71 | 16.4 | 43.4 | 5340 | 108 | 20.2 | 61.2 | 5656 | 7 | 1.24 | 2.57 |
| 40—44 | 4190 | 82 | 19.6 | 62.1 | 4653 | 91 | 19.6 | 79.6 | 5287 | 7 | 1.32 | 3.23 |
| 45—49 | 4039 | 77 | 19.1 | 80.0 | 4388 | 66 | 15.0 | 93.4 | 4912 | 8 | 1.63 | 4.09 |
| 50—54 | 3441 | 46 | 13.4 | 92.3 | 4137 | 80 | 19.3 | 110.8 | 4435 | 7 | 1.58 | 4.82 |
| 55—59 | 2617 | 23 | 8.8 | 100.3 | 3437 | 48 | 14.0 | 123.2 | 3576 | 1 | 0.28 | 4.96 |
| 60—64 | 1828 | 12 | 6.6 | 106.2 | 2492 | 31 | 12.4 | 134.0 | 2658 | 1 | 0.38 | 5.15 |
| 65—69 | 1364 | 3 | 2.2 | 108.2 | 1626 | 13 | 8.0 | 140.9 | 2059 | 1 | 0.49 | 5.39 |
| 70—74 | 934 | — | — | — | 1091 | 2 | 1.8 | 142.4 | — | — | — | — |
| 15—74 | | 457 | | | | 705 | | | | 59 | | |

The risk in the earlier period, i. e. the years 1929—33, increases gradually up to an age of between 40 and 50 years, and abates after that time. (For 5 persons information concerning age is lacking). The total risk at the age of 70 is 10.8 %. Also, with regard to the later group, the maximum risk seems to lie between 40 and 50 years of age. The irregularities prevailing in the figure series are probably due to variation at random. The total risk figure is 14.2 % in the later period. For the sake of comparison, it may be propounded that in Stockholm the risk for the period 1926—30 was 12 % and, during the period 1931—35, 8.6 %. The figures indicate that conditions, at present, are more serious in

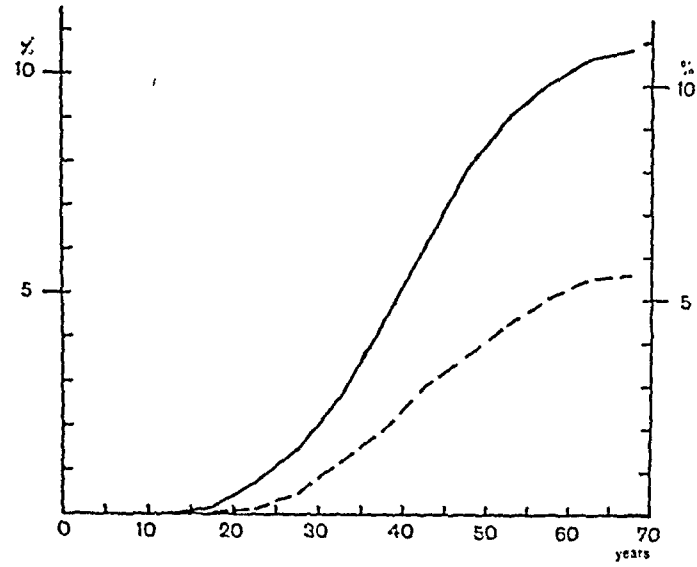



*Fig. 1.* The frequency of alcoholics in Malmö 1929—33. The whole line shows the number of men at different ages being taken care of at least once, the dotted line the number of men being interned.

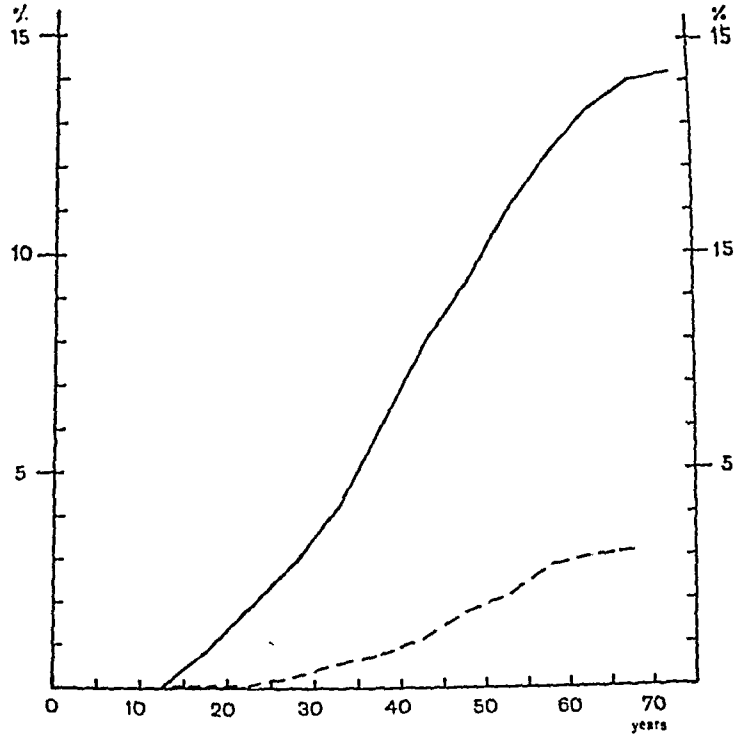



*Fig. 2.* The frequency of alcoholics in Malmö 1934—38. The whole line shows the number of men at different ages being taken care of at least once, the dotted line the number of men being interned.

Malmö than in Stockholm. Naturally, it is impossible to make a statement regarding the causes in this connection. Malmö has, perhaps, a traditional attitude towards alcohol differing from that of Stockholm. Also, maybe, the short distance from Copenhagen is of some significance. Social-economic conditions of various kinds may, possibly, exert an influence. In any case, it is impossible to make a definite statement without having the benefit of more comprehensive investigations than those performed by the author.

The risk for women in Malmö amounts only to 0.5 %, corresponding, approximately, to the Stockholm figure of the period 1931—35 which was 0.6 %.

These figures appear to be incredibly high. An approximate rough estimate will be made in order to show that the calculations are not preposterous. The culmination of the risk at about the age of 40 should be kept in mind. Accordingly, on an average, persons reported in 1935 were born in 1895, some after and others before that year. Moreover, 1,465 children were born that year in Malmö, 763 of which were boys. 16 % of the boys will probably die. Thus, 641 will reach the age of 40. Now, when 14 % are taken care of by the Temperance Board, this means that 90 persons are detained annually. In Table 1 the real figure will be seen to be substantially higher which is due, *inter alia*, to the fact that some people have immigrated into Malmö.

In consideration of this point, inebriates may, perhaps, be suspected of moving in to the cities to an especially great extent. Consequently, a migration of partly alcoholized individuals may be the reason of the high figures. With regard to Stockholm, the present author has been able to deny this. An investigation of conditions in Malmö reveals that the natives are detained as much as the immigrants.

The calculations have been performed in the following way: With the help of the Census of 1930 and with regard to the age distribution of the material, the percentage of inebriates who were natives was determined, if the material was of the same composition as the population of the town of Malmö in the corresponding ages. The figure for the period 1929—38 was 38.4 %, and the observed figure was 35.5 %. The difference is $2.9 \pm 2.0$ % and, consequently, is not statistically significant. As regards the women, the corresponding figures are 35.9 % and 27.6 %. The difference is

8.3 ± 8.6 %. Still, the birth-place of part of the material is unknown. Also, there is reason to conclude that some of these people were born in Malmö. If this is assumed to have occurred in a third of the cases, a not improbable supposition, the observed figures will be 38.3 % with regard to the men, and for the women 30.5 %, the difference being still less.

In considering the figures, it should be kept in mind, 1), that the inebriates belonging to the upper classes are, to a great extent, taken care of privately, as already mentioned. Thus, these figures are a little too low. Furthermore, 2), persons are often taken care of on account of alcoholism only after having been deeply degraded and socially unfit for a long space of time. In other words, some people die or have time to emigrate before they are subjected to detention. Finally, 3), as mentioned above, inebriates who have lived in Malmö and have been taken care of there, but have not been registered in that town, have been sorted out. But alcoholics registered in Malmö but taken care of elsewhere have not been included. For these reasons, the figures are decidedly too low. It is here a matter of pronounced minimum figures.

With a view to further differentiating the character of the material, this has been grouped in accordance with the degree of seriousness, with the help of the particulars noted by the Board at the first report. The cases have been classified in 4 groups, viz., doubtful cases, warned cases, supervised cases and interned cases. The classification of the material into these groups is illustrated in Table 3. 5 % of the 457 cases, reported during the period 1929—33,

**Table 3.**

Distribution in regard to the measures taken by the Board at the first report.

| Year | Doubtful at the first report | | Warned at the first report | | Supervised at the first report | | Interned at the first report | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % | Number | % | |
| | | | | Men: | | | | | |
| 1929—1933 | 23 | 5.03 | 257 | 56.24 | 94 | 20.57 | 83 | 18.16 | 457 |
| 1934—1938 | 55 | 7.80 | 383 | 54.33 | 182 | 25.82 | 85 | 12.06 | 705 |
| 1929—1938 | 78 | 6.71 | 640 | 55.08 | 276 | 23.75 | 168 | 14.46 | 1162 |
| | | | | Women: | | | | | |
| 1929—1938 | 8 | 13.56 | 23 | 38.98 | 22 | 37.29 | 6 | 10.17 | 59 |

were doubtful, not quite 60 % were only warned, about 20 % were supervised and an approximately equal amount were interned. The group of doubtful cases, consisting of 23 persons, comprises 8 individuals whose whereabouts were unknown. These persons might very well have been pronounced alcoholics. In addition, the report was withdrawn in 2 cases and another 2 cases had been admitted for care at a hospital. The remainder constitutes persons concerning whom the Board was undecided, and omitted to take definite steps. More than 2/3 of the doubtful cases in this period have since been reported a second time, and, in most instances, vigorous measures have then been adopted. As regards the period 1934—38 similar conditions prevail. Among the doubtful cases, viz., 55 persons, 10 were not to be found and 21 had been taken care of by another authority or institution; the report was withdrawn in 4 cases. The doubtful cases have increased somewhat, i. e. to not quite 8 %, but those interned have decreased to 12 %. The warned cases still form the majority, i. e. about 54 %. Supervision is now performed to a somewhat greater extent, that is to say, in almost 26 % of the material. The reports against the doubtful individuals have been repeated in half of the cases. However, the figure for recidivism is lower in this period which is, of course, dependent to some extent on the fact that the observation time is too short. Those reported and termed doubtful, in 1938, have, in all likelihood, not had time to incur a renewed report as the present investigation terminated in that year.

For the sake of completeness, it may be pointed out that with regard to women conditions are similar to those of men. During the whole of the period 1929—38, the doubtful persons comprised 8 cases, viz., 13.6 %, the warned ones 39.0 %, the supervised ones 37.3 % and those interned 10.2 %. Finally, a conception of the risk of being detained and interned at the first report would be of interest. With regard to men at the age of 70, this risk amounts to a total of 2.1 % during the period 1929—33, and, during the period 1934—38, it equals 2.0 %. These are lower than the figures given in the abovementioned work concerning the Stockholm material. However, the figures are not quite comparable. In the Stockholm material the risk of at all being interned in the course of a lifetime has been ascertained, while, in the Malmö material, the risk of being interned at the first report has been determined. Several of

those not interned then have been so later. Thus, the figures now presented denote only that part of the risk which refers to the first report and, consequently, the figures are lower.

However, also the total risk of being interned, during the course of a lifetime, has been determined in the Malmö material, irrespective of whether internment occurred in connection with a first or second report. Accordingly, during the first period 1929—33, this risk with regard to men will be found to equal 5.5 % and, during the second period, 3.1 %. The lower figures in the later period are, of course, due to the fact that too short a space of time has elapsed. Several of those reported in this group will be interned in the event of a relapse. When these figures are compared with those of Stockholm, the risk of seclusion will be seen to lie substantially lower than in Malmö. During the period 1926—30, the figure was in Stockholm 2.0 % and, during the period 1931—35, 2.3 %. With regard to the women in the Malmö material, the risk of internment, during the period 1929—38, was 0.2 % which corresponds to their low risk figure for alcoholism.

### *The risk of Alcoholism in Uppsala.*

An investigation has also been carried out into the risk of alcoholism in Uppsala, based on the risk figures for fifteen years e. g. 1922—1936. The result is shown in Table 4 and Fig. 3.

**Table 4.**

The risk for a man in Uppsala of being reported by the Temperance Board and the risk of being interned 1922—1936.

| Age | Risk of being reported during 10 years | Cumulative number in 1000 individuals | Risk of being interned | Cumulative number in 1000 individuals |
|---|---|---|---|---|
| 15—25 | 5.82 | 5.82 | 0.54 | 0.54 |
| 25—35 | 17.01 | 22.73 | 2.91 | 3.45 |
| 35—45 | 15.14 | 37.53 | 3.68 | 7.22 |
| 45—55 | 21.10 | 57.84 | 6.39 | 13.47 |
| 55—65 | 7.67 | 65.06 | 0.67 | 14.12 |
| 65—75 | 8.08 | 72.62 | — | 14.12 |
| 75—85 | — | 72.62 | — | 14.12 |

The total risk of one Uppsala inhabitant's being reported to the Temperance Board and considered an alcoholic is 7.3 %. The risk of being put under restraint is 1.4 %. There is no doubt that the risk figure is considerably lower for Uppsala than for Malmö, and that it is also lower in Uppsala than in Stockholm. It is of course impossible to determine exactly how far the differences between

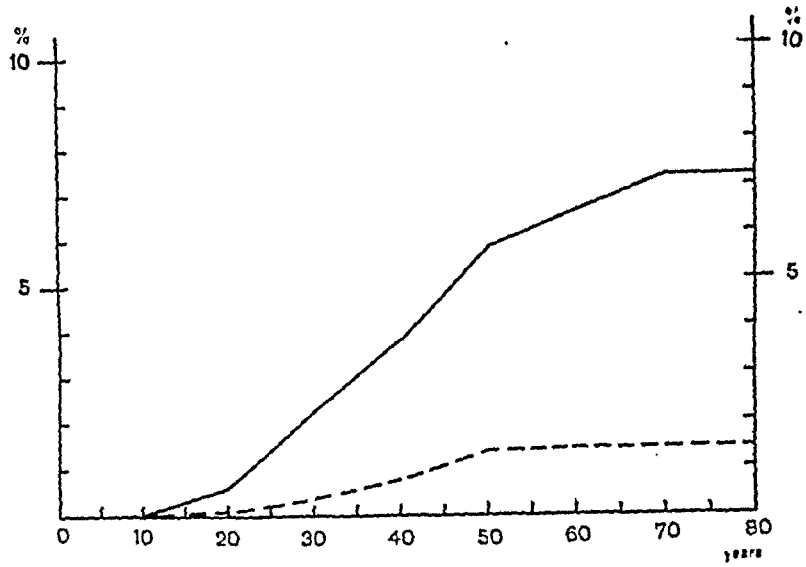



*Fig. 3.* The frequency of alcoholics in Uppsala 1922—36. The whole line shows the number of men at different ages being taken care of at least once, the dotted line the number of men being interned.

the risk figures for the different localities are actually true, and how far they are apparent and conditioned by the fact that application has been made to the Temperance Board to different extents. As regards Malmö, it may be stated that the figures for the number reported during the years 1939—1940 are 254 and 359 respectively. A comparison with Table 2 shows that the number reported during these years has clearly increased. This indicates that the risk figure to which our investigation refers does not, as regards Malmö, show a maximal effectiveness on the part of the Temperance Board. The risk figure must of course have risen further after our investigation was completed. We cannot, however, altogether exclude the possibility of the differences between the different localities being more apparent than actual. Going on personal knowledge of the circumstances, I am nevertheless most nearly inclined to say that it is quite impossible for the difference between Uppsala and Malmö, for example, to depend in the main on

different degree of activity of the Boards. The difference between Stockholm and Uppsala is of a more moderate size, and it is not possible to make any definite pronouncement on this point. For general reasons one should expect that the risk of alcoholism is greatest in the larger towns, lower in smaller towns and lowest of all in the country. The prohibition system is most effective in rural regions and less so in towns, where bars and restaurants are available. In addition, and particularly for the large towns, there has been the clandestine sale of spirits, which earlier on was undoubtedly more considerable than what it probably is nowadays. There are no figures allowing of a verification of this supposition, and it should be firmly stated that even if, on an average, differences of the kind assumed should be found, this still does not exclude the fact that a number of localities show appreciable divergences. For if we examine the frequency of the offence of drunkenness, we find great differences between different Swedish towns, and it is after all not out of the question that considerable differences could be ascertained as regards the risk of alcoholism also.

## Measures adopted by the Temperance Board.

Now, from a practical point of view, it is of interest to ascertain in what way the measures taken by the Temperance Board have caused the desired effect. Unfortunately, it is impossible to procure data regarding the extent to which persons taken care of can be restored to a normal manner of living, for a shorter or longer time. The reported persons have not been observed continuously. The only data in existence are of a negative kind. That is to say, figures are to be found revealing how often people reported once are liable to repeated charges. However, when a person has not been subjected to repeated reports, this may be attributable to his having moved to another place. It may be assumed that inebriates, submitted to intervention, rather often find it suitable to change their place of residence. Undoubtedly, many people do not find it agreeable to remain after having been dealt with more or less publicly. They prefer to change their abode to a place where nobody knows anything about them. Relatively often, drunkards are unemployed, which compels them to seek work not only in Malmö but also else-

where. This tendency is counteracted, to some degree, by the fact that inebriates may be expected to have difficulties in finding new employment, as they are not very diligent. In any case, there is reason to suppose that new reports occur to a much lesser extent than failure to improve or relapse. Therefore, the figures must be regarded as minimum figures.

In a comparison between the two periods, the most important difference with regard to the Board's procedure is, on the one hand, that internment has been imposed upon the reported persons to a somewhat lesser extent in the later period than in the earlier one. On the other hand, they have had to submit to supervision to a correspondingly greater extent. Possibly, this is due to an increase in the staff of the Board which has enabled supervision to be practised more frequently.

In order to acquire a general idea of the effect of the activity of the Temperance Board, the frequency of recidivism will be examined. In this connection, it should be kept in mind that a certain space of time must, of course, elapse before a person who has been reported once may be liable to a second misdemeanour and report. Only cases with comparatively long observation time are of any interest. For this reason, also here, the material has been divided into two periods, viz., cases during the years 1929—33 (the earlier period) and cases in the years 1934—38 (the later period). The figures of the later period are of little interest on account of the short observation time. They are only presented for the sake of completeness.[1]

Now, manifestly, during the earlier period, 81 % of the cases were reported a second time (cp. Table 5). 63 % of those reported twice were subjected to a third complaint and 58 % of those reported a third time were again taken care of. In other words, the relapsing frequency is extremely high. As has been pointed out above, the fact must be kept in mind that there is, in all probability, a certain tendency among those reported to change their place of residence in order to evade repeated intervention. In addition, removal owing to death also has to be taken into account. The

[1] It would have been possible to arrive at certain conclusions on the basis of the figures of the later period by means of a more comprehensive analysis. However, the results were not expected to compensate for the extra work entailed.

**Table 5.**

Frequency of recidivism.

| | Men | | | Women |
|---|---|---|---|---|
| | 1929—33 | 1934—38 | 1929—38 | 1929—38 |
| Reported at least once | 457 | 705 | 1162 | 59 |
| » » » twice | 369 | 284 | 653 | 26 |
| » » » » in per cent of the number reported once | 80.7 | 40.3 | 56.2 | 44.1 |
| Reported at least three times | 234 | 85 | 319 | 13 |
| » » » » » in per cent of the number reported twice | 63.4 | 29.9 | 48.9 | 50.0 |
| Reported at least four times | 136 | 20 | 156 | 3 |
| » » » » » in per cent of the number reported three times | 58.1 | 23.5 | 48.9 | 23.1 |
| Reported at least five times | 64 | 2 | 66 | 2 |
| » » » » » in per cent of the number reported four times | 47.1 | 10.0 | 42.3 | 66.7 |
| Reported at least six times | 25 | — | 25 | — |
| » » » » » in per cent of the number reported five times | 39.1 | — | 37.9 | — |
| Reported at least seven times | 11 | — | 11 | — |
| » » » » » in per cent of the number reported six times | 44.0 | — | 44.0 | — |

last-mentioned fact plays a greater part when reporting in higher ages is examined. In consideration of the fact that 40 is the mean age with regard to reports, a not inconsiderable mortality figure in the material must be reckoned with. The figures are minimum ones, inasmuch as the longest observation time is 10 years and the shortest is 5 years. If the observation time had been longer, e. g., 10 years throughout the material, the figures would have been higher. As regards women, the calculated figures comprise too small a number of cases to permit the drawing of conclusions.

The high frequency figure of repeated reports serves to show that the result of intervention by the Temperance Board is not very brilliant. In order to gain a more differentiated conception of conditions, the cases have been divided with regard to the kind of procedure adopted at the first report.

*Doubtful cases at the first report.*

This group embraces cases which gave definite reason to believe that the person in question was addicted to alcohol. However, the Temperance Board did not adopt special measures in these cases. The reason was, for instance, that the whereabouts of the person concerned were unknown, or he had been taken care of by another institution or, again, in a few cases, the Board had hesitated, as a matter of fact, concerning the suitability of interference. The motive had been that the individual was either too young or for other reasons was regarded with a certain amount of optimism.

**Table 6.**

Doubtful cases at the first report with regard to a second report and measures then taken.

| Year | Doubtful at the first report | Reported a 2nd time | The latter in % of the first | Measure at the second report | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No measure | | | | Warned | | Supervised | | Interned | |
| | | | | Not addicted | | Doubtful | | | | | | | |
| | | | | Number | % | Number | % | Number | % | Number | % | Number | % |
| | | | | Men: | | | | | | | | | |
| 1929—1933 | 23 | 17 | 73.9 | — | — | 2 | 11.8 | 3 | 17.6 | 7 | 41.2 | 5 | 29.4 |
| 1934—1938 | 55 | 26 | 47.3 | — | — | 5 | 19.2 | 12 | 46.2 | 4 | 15.4 | 5 | 19.2 |
| 1929—1938 | 78 | 43 | 55.1 | — | — | 7 | 16.3 | 15 | 34.9 | 11 | 25.6 | 10 | 23.3 |
| | | | | Women: | | | | | | | | | |
| 1929—1938 | 8 | 2 | 25.0 | — | — | — | — | — | — | 2 | 100.0 | — | — |

In 74 % of the cases the person concerned is reported again and, then, as a rule, proceedings are carried into effect (cp. Table 6). In 29 % of the cases internment is enforced, in 41 % supervision, etc. Now, it is, of course, too optimistic to assume that cases not subjected to repeated reports, or against whom no measure has been taken at the second report, are to be considered as restored to a normal manner of living. It is natural that, among those not reported again, there must be several who have moved to another place, etc. In other words, a maximum figure for improvement is obtained. 38 % belong to this group. However, in two thirds of these cases the person in question continued to misbehave after

the first report. No doubt, in many of these cases, it would have been appropriate for the Board to have intervened more strictly. Finally, the figures emphasize the legitimate in also counting the group of cases characterized as doubtful as real alcoholics.

### *Warned cases at the first report.*

87 % are reported again and, in the majority of cases, they are the object of repeated warnings (42 %), supervision (32 %) or internment (18 %). When, also here, those not subjected to repeated reports, and those against whom definite measures have not been adopted at the second report, are regarded as improved, the figure 21 % will be obtained which is, of course, an extremely low figure.

**Table 7.**

Warned at the first report with regard to a second report and measures then taken.

| Year | Warned at the first report | Reported a 2nd time | The latter in % of the first report | Measure at the second report | | | | | | | | | | Doubtful + warned at the 2nd report | Reported a third time | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No measure | | | | Warned | | Supervised | | Interned | | | | |
| | | | | Not addicted | | Doubtful | | | | | | | | | | |
| | | | | Number | % | Number | % | Number | % | Number | % | Number | % | | Number | % |
| | Men: | | | | | | | | | | | | | | | |
| 1929–1933 | 257 | 224 | 87.2 | 2 | 0.9 | 17 | 7.6 | 93 | 41.5 | 72 | 32.1 | 40 | 17.9 | 110 | 71 | 64.5 |
| 1934–1938 | 383 | 178 | 46.5 | 3 | 1.7 | 11 | 6.2 | 67 | 37.6 | 74 | 41.6 | 23 | 12.9 | 78 | 22 | 28.2 |
| 1929–1938 | 640 | 402 | 62.8 | 5 | 1.2 | 28 | 7.0 | 160 | 39.8 | 146 | 36.3 | 63 | 15.7 | 188 | 93 | 49.5 |
| | Women: | | | | | | | | | | | | | | | |
| 1929–1938 | 23 | 7 | 30.4 | — | — | 1 | 14.3 | 1 | 14.3 | 4 | 57.1 | 1 | 14.3 | — | — | — |

The warned cases have worse future prospects than those regarded as doubtful. Nevertheless, with regard to both groups, it is mostly to be expected that the person concerned will have to be taken charge of again. Table 7 also gives figures illustrating what has happened to those considered as doubtful or only warned. 65 % of these cases have been reported a third time and have, then, in more than half of the cases, been subjected to stricter methods. Still, in 35.2 % it has been considered sufficient only to warn the individual. In other words, it is evident that the Temperance Board has

great patience and avoids interference as far as possible. As a matter of fact, the figures give the impression that the adoption of more severe steps would have been more appropriate at the very first report and, likewise, in the event of a second report.

Finally, it is of interest to note the age distribution among those warned at the first report (Table 8). It will be seen that 90 % reappear at the age of 30—40 years and, further, that the figures for the group 20—60 years of age remain at a higher level than for the groups under 20 and over 60 years. The fact that the 20-year-olds have lower figures is, probably, to be connected with the comparatively frequent moving at this age. In this group, it is especially to be expected that the person in question departs to another place. The fact that repeated reports decrease with regard to the older individuals is probably, partly, owing to the prevailing high mortality in this group, and partly, to their being taken care of at homes for the aged.

**Table 8.**

Warned at the first report with regard to age.
Men 1929—1933.

| Age at the 1st report | All cases | Cases reported twice | |
|---|---|---|---|
| | | Number | % of total |
| —19 | 5 | 3 | 60.00 |
| 20—29 | 49 | 43 | 87.76 ± 4.7 |
| 30—39 | 77 | 70 | 90.91 ± 3.3 |
| 40—49 | 83 | 71 | 85.54 ± 3.9 |
| 50—59 | 34 | 31 | 91.18 ± 4.9 |
| 60—69 | 9 | 6 | 66.67 |
| Total | 257 | 224 | 87.16 ± 2.1 |

*Supervised cases after the first report.*

68 % of the supervised cases reappear and are subjected to renewed intervention. When those who do not reappear, or are not subjected to definite intervention, in the event of repeated reports, are still regarded as improved, the maximum figure for the improved cases will be 38 %. Supervision seems to have a better effect than warning. There is reason to suppose that, if the Board had resorted to supervision in the case of doubtful and only warned persons,

Table 9.

Supervised at the first report with regard to a second report and measures then taken.

| Year | Supervised at the 1st report | Reported a 2nd time | The latter in % of the 1st report | Measure at the 2nd report | | | | | | | | Doubtful + warned at the 2nd report | Reported a 3rd time | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No measure | | | | Warned | | Supervised | | Interned | | | | |
| | | | | Not addicted | | Doubtful | | | | | | | | | | |
| | | | | Number | % | Number | % | Number | % | Number | % | Number | % | | Number | % |
| | | | | Men: | | | | | | | | | | | | |
| 1929-1933 | 94 | 64 | 68.1 | 1 | 1.6 | 3 | 4.7 | 19 | 29.7 | 25 | 39.1 | 16 | 25.0 | 22 | 11 | 50.0 |
| 1934-1938 | 182 | 56 | 30.8 | 1 | 1.8 | 8 | 14.3 | 10 | 17.9 | 18 | 32.1 | 19 | 33.9 | 18 | 8 | 44.4 |
| 1929-1938 | 276 | 120 | 43.5 | 2 | 1.7 | 11 | 9.2 | 29 | 24.2 | 43 | 35.8 | 35 | 29.2 | 40 | 19 | 47.5 |
| | | | | Women: | | | | | | | | | | | | |
| 1929-1938 | 22 | 14 | 63.6 | — | — | 2 | 14.3 | 1 | 7.1 | 8 | 57.1 | 3 | 21.4 | — | — | — |

the result would have been better. It will be seen, in table 9, that the person concerned is reported a third time in 50 % of the cases which have been supervised at the first report but, at the second report, have been regarded as doubtful or only warned.

*Interned cases at the first report.*

The cases interned at the first report are undoubtedly a group of very serious instances of alcoholism. 72 % are subjected to repeated reports (cp. Table 10). It is noteworthy that the Board has considered 8 cases to be doubtful at repeated reports and only resorted to warning in 12 cases. This suggests a definite improvement in these cases, as not even supervision has been considered necessary. Thus, this group comprises 24 % of the cases interned at the first report. When the maximum figure of those improved is again calculated, 41 % is obtained. In other words, the impression is given that internment has a better effect than supervision and warning. The prospect of reforming an alcoholic is, apparently, greater if he is treated with a certain degree of severity rather than leniently. However, in order to be able to draw an absolutely definite conclusion, it is necessary to examine the reason why the person concerned has not been subjected to repeated reports and, then, especially the degree to which change of residence occurs. In any

**Table 10.**

Interned at the first report with regard to a second report and measures then taken.

| Year | Interned at the 1st report | Reported a 2nd time | The latter in % of the 1st report | Measure at the 2nd report: No measure: Not addicted: Number | Not addicted: % | Doubtful: Number | Doubtful: % | Warned: Number | Warned: % | Supervised: Number | Supervised: % | Interned: Number | Interned: % | Doubtful + warned at the 2nd report | Reported a 3rd time: Number | Reported a 3rd time: % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Men:** | | | | | | | | | | | | | | | | |
| 1929–1933 | 83 | 60 | 72.3 | — | — | 8 | 13.3 | 12 | 20.0 | 11 | 18.3 | 29 | 48.3 | 20 | 11 | 55.0 |
| 1934–1938 | 85 | 23 | 27.1 | — | — | 2 | 8.7 | 8 | 34.8 | 2 | 8.7 | 11 | 47.8 | 10 | 5 | 50.0 |
| 1929–1938 | 168 | 83 | 49.4 | — | — | 10 | 12.0 | 20 | 24.1 | 13 | 15.7 | 40 | 48.2 | 30 | 16 | 53.3 |
| **Women:** | | | | | | | | | | | | | | | | |
| 1929–1938 | 6 | 3 | 50.0 | — | — | — | — | — | — | 2 | 66.7 | 1 | 33.3 | — | — | — |

case, the figures do not offer any support to the assumption that lenient methods as a rule are advantageous in the long run. It may be pointed out that half of the cases considered to be doubtful or only warned at the second report are subjected to a repeated report. In half of these cases the person is subjected to internment.

**Table 11.**

Frequency of repeated internments.

| | Men | | | Women |
|---|---|---|---|---|
| | 1929—33 | 1934—38 | 1929—38 | 1929—38 |
| Reported | 457 | 705 | 1162 | 59 |
| Interned at least once | 220 | 138 | 358 | 13 |
| » » » » in per cent of the number reported | 48.1 | 19.6 | 30.8 | 22.0 |
| Interned at least twice | 88 | 17 | 105 | 5 |
| » » » » in per cent of the number interned once | 40.0 | 12.3 | 29.3 | 38.5 |
| Interned at least three times | 30 | 2 | 32 | — |
| » » » » » in per cent of the number interned twice | 34.1 | 11.8 | 30.5 | — |
| Interned at least four times | 5 | — | 5 | — |
| » » » » » in per cent of the number interned three times | 16.7 | — | 15.6 | — |

In order further to illustrate internment, the frequency of repeated internments is given in Table 11. 40 % of interned cases are detained a second time and 34 % of these are subjected to internment a third time in the earlier period.

*Summary in regard to treatment of alcoholics.*

The above-mentioned figures illustrate the fact that the relapsing frequency is very high among alcoholics. This also concerns cases which have been considered doubtful or only warned by the Temperance Board. In other words, it is desirable that measures are taken to obtain better results. The figures stated mostly indicate that the Board should adopt vigorous measures to a more extensive degree. It is natural that a warning should be ineffective. An alcoholic does not change his way of living without cause. That he is inefficient in his work, that acquaintances shun him and that his family finds him intolerable has not made him give up drinking. It is evident that a more or less solemn warning from a Temperance Board cannot often have any lasting effect. Supervision should be imposed more frequently with regard to mild forms of alcoholism. Cases should not be dismissed, and the person in question should not be regarded as doubtful to the extent hitherto done. Furthermore, the Board should not content itself with administering warnings quite so often. In many instances, warning is an emergency step owing to the staff of the Board being insufficient in number to permit effective supervision of a considerably greater number of individuals. At all events, it is here a question of a very unremunerative form of economization on the part of the society. If one or two extra officials were employed and supervision could be enacted more extensively, it is probable that expenses for the custody of a not inconsiderable number of persons would be spared. With regard to internment the present author has already propounded that a special institution for short time internment should be established. Certainly the conception that long internment must have a favourable effect is not very well-grounded. An inebriate can never be restored to a normal manner of living if it has not been possible to inculcate upon him a desire to give up alcohol. The idea that a long period of internment is more favourable than a short one is, no doubt, to be connected with

the fact that alcoholism is regarded as a disease. Therefore, it is believed that the prospects of recovery are greater the longer the time during which the afflicted person is taken care of. Manifestly, it is necessary that the individual taken charge of is permitted to sober down, and have time to think matters over, and reflect whether it is not too risky to continue in the same manner as before. In this connection, the satisfaction felt in becoming intoxicated has to be weighed against the troubles incurred when the craving is appeased. It will hardly make a great difference whether the individual is allowed to meditate on this point for a whole year or only for a month or two. The possibility, then, remains that the desire for alcohol will diminish with time. Nevertheless, this does not seem probable. During a long period of enforced continence, sober habits are formed which are opposed to those acquired during a much longer time and which resulted in alcoholism. Still, the new habits are connected with altogether specific surroundings and a life adjusted to definite rules. When the person in question leaves the institution he returns to an environment where it is customary to drink alcohol. Of course the person has not acquired a habit of saying »no» and abandoning alcohol in this environment. Habits imprinted in this way are, no doubt, very scanty protection, if the person in question has not, besides, made a firm decision to change his manner of living, based on the fact that he has realized clearly that he is heading for serious trouble. A single adversity or difficulty, deranging his balance of mind, will make him feel that the sense of elation caused by alcohol may withdraw the depression. In reality, however, after having taken up drinking again an inebriate need not continue for years before reaching the stage at which he had to be interned. He becomes the same degraded drunkard as before, after a very short space of time. As far as the author can see, this argues the point that lengthy internment does not involve constitutional improvement. Internment for a long period of time, when the person concerned comes into contact with comrades, many of whom are old degraded inebriates without a thought of improving, cannot affect him altogether favourably. As a rule, a bad influence is of far greater consequence than a good one.

From a social point of view, warning or supervision are comparatively mild proceedings which do not interfere with the individual's life in other ways than with respect to abuse of alcohol

whereas internment for a long period of time is quite a different matter. Then, the individual is separated from his family. His presence at a Home for Inebriates cannot be concealed. Furthermore, in many cases, he loses his work, even if there are examples of kind-hearted employers who let these individuals keep their jobs. When an alcoholic has been interned for a long stretch of time difficulties often confront him on his release. He feels conspicuous and he has a hard time finding work. Then, it is natural that he should turn to drink to find comfort in his misery and to experience a moment's light-heartedness.

Apparently, in many cases, supervision is too lenient a procedure, while long internment is too severe. Therefore, I have suggested that short term internment should be organized at a special institution for a period of two months, at the most. Then, the person concerned would have time to sober down and think things over. Moreover, it would be possible to conceal his stay at the institution. Also, it would be easier to arrange for him to be permitted to keep his work. He would not come into contact with degraded inebriates, interned for the second or third time, to whom the institution is nothing but a sanatorium where one gathers strength for new excesses. This proposition was put forward as early as in 1934. It has not met with public opposition or criticism, but, on the other hand, it has not been accepted by the authorities.

## The social character of the alcoholics.

From a social point of view, alcoholics are characterized by the fact that they can no longer perform the minimum claims laid upon them as citizens owing to misuse of alcohol. For many reasons, it is impossible to obtain statistical support to an illustration of the defects manifested by alcoholics. The moral incorrigibility and want of consideration displayed at their work, in company during spare time, and in their family life, entails only gradually consequences of a more definite character. Viz., they are dismissed from their jobs, they are convicted for drunkenness and, furthermore, they are disorderly, and are sentenced for assault and battery or other crimes. Before entering upon these sides of the social character of inebriates, a short survey of the material with regard to age, sex, civil status and occupation will be delivered.

## *Age.*

The age distribution among the alcoholics at the time of the first report will be seen in Table 12. The frequency of reported men slowly rises up to the age of 40, only to fall slowly after that age.

**Table 12.**

Age at the first report.

| Age | Men 1929—33 | | | | | Men 1934—38 | | | | | Women 1929—38 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Doubtful | Warned | Supervised | Interned | Total | Doubtful | Warned | Supervised | Interned | Total | Doubtful | Warned | Supervised | Interned | Total |
| 15—19 | 1 | 5 | 1 | — | 7 | 7 | 37 | 4 | — | 48 | — | — | 1 | — | 1 |
| 20—24 | 2 | 24 | 5 | 2 | 33 | 10 | 49 | 6 | 2 | 67 | 1 | 2 | 2 | 1 | 6 |
| 25—29 | 2 | 25 | 8 | 8 | 43 | 3 | 40 | 24 | 2 | 69 | 2 | 3 | 2 | — | 7 |
| 30—34 | 1 | 32 | 13 | 14 | 60 | 3 | 46 | 20 | 13 | 82 | 3 | 6 | 3 | 1 | 13 |
| 35—39 | 2 | 45 | 11 | 13 | 71 | 9 | 57 | 34 | 8 | 108 | — | 5 | 2 | — | 7 |
| 40—44 | 5 | 40 | 20 | 17 | 82 | 5 | 46 | 27 | 13 | 91 | — | 2 | 5 | — | 7 |
| 45—49 | 4 | 43 | 18 | 12 | 77 | 5 | 24 | 21 | 16 | 66 | — | 3 | 2 | 3 | 8 |
| 50—54 | 3 | 25 | 9 | 9 | 46 | 4 | 44 | 21 | 11 | 80 | 2 | — | 4 | 1 | 7 |
| 55—59 | 3 | 9 | 8 | 3 | 23 | 5 | 16 | 14 | 13 | 48 | — | — | 1 | — | 1 |
| 60—64 | — | 6 | 1 | 5 | 12 | 3 | 16 | 7 | 5 | 31 | — | 1 | — | — | 1 |
| 65—69 | — | 3 | — | — | 3 | 1 | 7 | 3 | 2 | 13 | — | 1 | — | — | 1 |
| 70—74 | — | — | — | — | — | — | 1 | 1 | — | 2 | — | — | — | — | — |
| 15—74 | 23 | 257 | 94 | 83 | 457 | 55 | 383 | 182 | 85 | 705 | 8 | 23 | 22 | 6 | 59 |

The fact that the mean age at the time of the first report is as high as 40 years is a matter worthy of attention. This implies that the individual has often been misusing alcohol for more than a decennium, before reaching the state at which he was reported to the Temperance Board because of incorrigibility. In this connection, it may be noted, regarding the risk of being sentenced for drunkenness, that the maximum risk lies at about the age of 25, according to the author's earlier investigation concerning conditions in Stockholm. The mean age in Stockholm is as high as 45 years, with regard to reports to the Temperance Board. The matter has been put forward as follows: The risk of being convicted for drunkenness is greatest at a young age when the hazard with regard to alcohol and the police is underestimated. The risk of being reported to the Temperance Board is greatest at an older age when an exten-

sive experience of alcohol and the police has been acquired. Moreover, it follows, as a matter of course, that when a young person gets drunk, more or less continuously, this is apt to be ascribed, at least partly, to the lack of common sense appertaining to youth. The matter is not considered to be as serious as in the case of middle-aged persons. It is believed to be a comparatively easy task to reform a young person to a more normal way of living. This is, doubtless, manifested by the fact that the Temperance Board is satisfied with lenient measures to a fairly great extent concerning young individuals. Quite often the case is considered doubtful or a warning is regarded as adequate. In this connection, the fact mentioned before may here be emphasized viz., the frequency of recidivism for doubtful cases or those warned is very high and repeated reports are to be expected in the majority of these cases. Certainly, optimism with regard to young alcoholics is far from always justifiable. On the contrary, it is to be expected that when a person conducts himself in his youth in a way leading to report to the Temperance Board, he is not a promising character. There is reason to resort to vigorous action in order to give the individual a more effective warning than that administered by the Temperance Board.

With regard to the very old a less strict procedure is thought to suffice. In many instances, perhaps, the case seems such a hopeless one that it is not worth the trouble to intervene.

### *Sex distribution.*

As has been mentioned before, the men comprise 95.2 % of the material. The risk figures submitted earlier afford the best basis for a comparison between the sexes. (Cp. Table 2) It is to be observed that the total risk, during the period 1929—33, for a man living up to the age of 70 years was 10.8 % and, for a woman, 0.5 %. Thus, the risk for women is 5 % of that of the men. The figures for the later period, 1934—38, are 14.2 % for the men. Here, the risk run by the women is 3.5 % of that of the men. Of course, this is partly to be explained by the difference in custom between men and women with regard to the use of alcohol. No doubt, also the economic difference plays a part in this connection. Under these circumstances, it is difficult to decide

the extent to which the constitutional disposition of women to fall for continuous abuse of alcohol differs from that of men. However, if a woman is reported to the Temperance Board, the risk of recidivism is about equal to that of a man.

### *Civil status.*

When a conception of the frequency of marriage is to be obtained divorced people as well as widows and widowers are included. The point of interest is whether alcoholism involves a change in the frequency of marriage. On the one hand, it may be suspected that the alcoholic habits of a young person should be founded on quali-

**Table 13.**

Frequency of married persons in the male population of Malmö in 1935 and in male alcoholics in Malmö 1929—1938.

| Age | The population of Malmö 1935 | Married divorced or widowers | % married in Malmö | 1929—1938 | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Alcoholics | Married alcoholics | % married | Married + cohabitating | % married + cohabitating |
| 15—19 | 5592 | 2 | 0.04 | 55 | — | — | — | — |
| 20—24 | 6217 | 510 | 8.2 | 100 | 20 | 20.0 | 24 | 24.0 |
| 25—29 | 6880 | 2815 | 40.9 | 112 | 72 | 64.3 | 83 | 74.1 |
| 30—34 | 6112 | 4212 | 68.9 | 142 | 96 | 67.6 | 102 | 71.8 |
| 35—39 | 5314 | 4301 | 80.9 | 179 | 133 | 74.3 | 140 | 78.2 |
| 40—44 | 4628 | 3943 | 85.2 | 173 | 137 | 79.2 | 147 | 85.0 |
| 45—49 | 4364 | 3817 | 87.5 | 143 | 113 | 79.0 | 121 | 84.6 |
| 50—54 | 4128 | 3615 | 87.6 | 126 | 95 | 75.4 | 99 | 78.6 |
| 55—59 | 3421 | 3039 | 88.8 | 71 | 55 | 77.5 | 60 | 84.5 |
| 60—64 | 2478 | 2201 | 88.8 | 43 | 34 | 79.1 | 35 | 81.4 |
| 65—69 | 1620 | 1459 | 90.1 | 16 | 12 | 75.0 | 14 | 87.5 |
| 70—74 | 1085 | 969 | 89.3 | 2 | 1 | 50.0 | 1 | 50.0 |

ties which diminish his or her possibilities of getting married. However, on the other hand, it may also be taken into account that alcoholism may be the manifestation of a lack of resistance in a person to temptations of different kinds and, consequently, also involves marriage to a comparatively great extent in these cases. It may be mentioned, in this connection, that the marriage frequency of delinquent girls who have been taken care of at institutions on account of sexual offences, later on, when they have left the insti-

tution, seems to be rather high and, at any rate, not lower than that of non-delinquent girls. Table 13 shows figures of the frequency of married persons in Malmö and in the alcoholic material. The frequency is higher among the inebriates in the younger groups than in the corresponding ages of the average population. This difference is erased at a higher age (after the age of 30) and, thereafter, the figures seem to lie on a somewhat lower level for the alcoholics.

In the material data will be found of the number of inebriates who live together in a state of cohabitation. If these cases are regarded as marriages, the figures for alcoholics of higher age come to lie almost on a level with those of the average population. However, the figures of cohabitation are not included in the population figures. If that was the case, the figures of comparison would, perhaps, be somewhat higher. Still, the figures reveal, to a certain degree, that young alcoholics regard themselves and are regarded by the opposite sex with some degree of optimism. No doubt, if there is any change at a more mature age, it will disclose the fact that habitual drunkenness somewhat diminishes the probability of entering into marriage but, still, the influence of age is not very distinct. The marriage frequency in Stockholm was somewhat lower among the alcoholics than in the average population.

Negative results have been obtained in an investigation concerning the difference between the internment frequency of married and unmarried people. No difference was ascertainable.

### *Trades and professions.*

It has been mentioned before that the inebriates in the well-to-do classes are detained by the Temperance Board to a fairly small extent. When the person concerned is well off, the possibility of arranging private care is quite often made use of. Easy circumstances have the effect that many reasons for intervention cease to exist. The rich person does not have to apply for public assistance and does not expose his family to neglect, etc. Therefore, it is natural that the majority of individuals belong to the lower classes, in a classification of the material into trades and professions. Those reported have been classified in the unqualified trades and the more qualified ones. The latter term denotes craftsmen, clerks, commercial travellers, railway officials, policemen, etc. A

third group comprises chiefly dock-workers, sailors, and persons in a trade bringing them into contact with alcohol, e. g., waiters and waitresses, and (prostitutes and) women who have only been married. As corresponding grouping according to occupations does not exist with regard to the whole population of Malmö, the figures offer little information, merely illustrating the above-mentioned fact that a very insignificant number of the upper classes have been represented. Therefore no table is given. However, it is of interest to examine the relative frequency of especially severe cases of alcoholism within these groups by means of ascertaining the frequency of internment. It has been found that the frequency of interned persons and those interned repeatedly is especially high with regard to the more qualified occupations and the sailors. The female material is too small to permit the drawing of conclusions.

The school education of the persons concerned is of greater interest. Alcoholics deriving from the upper classes who have been afforded a better education and, in some cases, have even passed the matriculation, may be expected to some extent to degrade themselves socially. Therefore, they come to belong to a lower class with regard to their occupation. Also, it has been revealed that the number of persons with secondary school education is comparatively great, i. e. 4.5 %, and the number of those with higher education, i. e. matriculation and, in some cases, continued studies, comprises 2.2 %. In total these two groups constitute 6.7 % of the material. The corresponding figure for the Stockholm material was 8 %. Both with regard to the Malmö and the Stockholm cases only a comparatively small number of those educated at secondary schools have passed matriculation, viz. only a fourth. This figure indicates that children of parents, who were in a position to send them to secondary schools, run a not altogether insignificant risk of becoming alcoholics. But, these cases consist mainly of children who have not been able to make use of their education, on account of laziness or lack of talent. In this connection, it should be kept in mind, that the more well-to-do inebriates are taken care of privately and fairly seldom pass the Temperance Board. That in spite of this nearly 7 % of the material is made up of individuals who have been at secondary schools indicates that also the children of the well-to-do are running a great risk when growing up. There

is hardly any reason to assume that in general the well-to-do should have better characters than the poor or react against alcohol in another way. It should be added that economical factors play a role because the poor cannot afford to buy alcohol to a very great extent and are more dependent on their capacity for work.

### *Capacity for work.*

An investigation with regard to the extent to which a person is continuously unemployed or out of work, for some reason or another, presents the result that those reported have work in most cases, viz., in 75 %. In this connection, it should be remembered that alcoholism with regard to labourers and simpler forms of work, on the whole, is not as fatal as in the more qualified occupations. Nevertheless, even when this circumstance is taken into account, the figures seem rather high. The fact that the individual is out of work may, of course, in some instances be due to his age. But only 20 % in this group are above 60 years of age and, consequently, 80 % of the unemployed are under the age of 60. With regard to the frequency of recidivism the group of unemployed seems to have the highest frequency of reports.

### *Public Assistance.*

A consequence of lowered capacity for work is that the person concerned has to receive assistance out of public funds. In many instances, the individual is supported by his relatives, but reliable figures of the frequency of this form of relief are non-existent. 36.7 % have either received public assistance or unemployment relief. In consideration of the measures adopted the group in receipt of public assistance seems to represent a more severe type of alcoholism. Thus, they are relatively often interned and seldom only warned. On the other hand, those receiving unemployment relief seem to be interned comparatively rarely. Only 22.4 % of the indigent alcoholics receiving relief are reported by the Poor Relief. It is, indeed, strange that the Poor Relief has not realized, to a greater extent, the unsuitability of only administering relief, and that it is also necessary to arrange for the person concerned to be taken charge of by the Temperance Board.

*Grounds for internment.*

Data concerning grounds for internment are to be found with regard to 327 men. It will be noted that in 231 cases only one ground for internment is stated, in the rest two or more reasons are given. 26.9 % were considered a danger to themselves or to the safety of others. Repeated cases of drunkenness occurred in 9.8 %, and disturbing manner of living in 2.1 % of the cases. In the remainder, viz., 61.2 %, the grounds for internment were of a more or less economical character. That is to say, the family was exposed to destitution or neglect, or the alcoholic was a burden to the community, or was incapable of taking care of himself. In spite of the fact that the inebriates have had work to a relatively great extent, the discovery that 36.7 % of them have been in receipt of public means, and that the internment grounds were of an economical character in 61.2 % of the cases, shows that the income they have been able to make has not sufficed to keep poverty away from the home. The situation is, most likely, to be explained by their lack of efficiency which involves a small income and, not rarely, an irregular one. In addition, the consumption of alcohol entails expenses of different kinds, directly or indirectly.

A special investigation has served to illustrate the existence of a correlation, i. e. if the same ground for internment exists at the first and later reports. As a rule, the reason will be identical in the event of a later internment.

*Offences committed concerning drunkenness after the first report.*

If the steps taken by the Temperance Board for the care of inebriates resulted in improvement throughout, no offences concerning drunkenness after a report would have to be expected. However, as has already been put forward, the effect of measures adopted by the Board is not brilliant, and repeated reports are likely in the majority of the cases. Thus, it is not surprising to find that alcoholics have been convicted for drunkenness in the period following upon the first report. During the period 1929—33, 42.5 % were not convicted, in the period 1934—38 the corresponding figure was 71.4 %. Now, the figures obtained are dependent on the extent to which the person in question has been subjected to obser-

vation. No information is given regarding persons who have not been reported again for drunkenness offences. An inquiry regarding the observation time discloses that in the group which has been watched for a long time (viz., averagely for 7 years) the risk per year and per inebriate is 0.35, i. e. on an average one offence every third year.

### *Alcoholism and criminality.*

Alcoholism may be the cause of a crime but, reversely, an individual with criminal tendencies may also, comparatively often, become a drunkard. He is a criminal even if he does not fall into habits of intemperance. However, it is most presumable that inebriates belong to the dregs of society and are criminal to a fairly

**Table 14.**

Alcoholics distributed with regard to crimes committed and frequency of recidivism.

| | Reported at least once | % of total reported | Reported at least twice | % of once reported | Reported at least 3 times | % of twice reported | Reported at least 4 times | % of 3 times reported |
|---|---|---|---|---|---|---|---|---|
| | Men 1929—38 | | | | | | | |
| Alcoholics sentenced for crime (drunkenness not included) .. | 313 | 26.9 | 185 | 59.1 | 107 | 57.8 | 45 | 42.1 |
| Alcoholics not sentenced (drunkenness not included) ..... | 849 | 73.1 | 468 | 55.1 | 212 | 45.3 | 111 | 52.4 |
| Total alcoholics | 1162 | 100.0 | 653 | 56.2 | 319 | 48.9 | 156 | 48.9 |
| | Women 1929—38 | | | | | | | |
| Alcoholics sentenced for crime (drunkenness not included) .... | 32 | 54.2 | 17 | 53.1 | 11 | 64.7 | 2 | 18.2 |
| Alcoholics not sentenced (drunkenness not included) ..... | 27 | 45.8 | 9 | 33.1 | 2 | 22.2 | 1 | 50.0 |
| Total alcoholics | 59 | 100.0 | 26 | 44.1 | 13 | 50.0 | 3 | 23.1 |

large extent. An orientation is presented in Table 14, revealing that 26.9 % of the drunkards have been convicted for at least one crime. (In this connection, however, sentence for drunkenness has not been included.) With regard to the frequency of recidivism,

this appears to be somewhat higher among criminal alcoholics than among individuals not convicted of a crime. Further, in the table, figures are given concerning the character of the offence. Thus, a person has been registered every time he has committed a crime and those who have perpetrated two or more crimes have, consequently, been entered a corresponding number of times. Vagrancy constitutes a third of the crimes. Thereafter, diverse crimes follow, such as, inter alia, fraud, sexual offences, etc. Then, thirdly, theft is committed in 23.2 %, and in the fourth place, assault and battery in 13.3 %. As regards the recidivists, no striking difference can be found, but it should be kept in mind that the groups are small. Vagrancy is the most important group of crimes as regards the women, comprising 82 %. Theft and other crimes constitute 9 %, respectively. It is noteworthy that 54 % of the women have been sentenced for crimes. In other words, the women reported for drunkenness have been warned or sentenced for vagrancy in the majority of the cases and belong to a socially very degraded group of people.

*Summary in regard to social character of alkoholics.*

The analysis of the material which has been performed, especially, with regard to the social character of the alcoholics can hardly be said to have offered any new and surprising results. On the whole, the Malmö material corresponds to that of Stockholm. Principally, people belonging to the lower classes are concerned. A not altogether insignificant group comprises individuals who have been in a position to attend public schools as children but finished school and did not reach the matriculation stage. The mean age is 40 years. The marriage frequency is, at any rate, not lower than that of the average population. The capacity for work is retained to a comparatively large extent. Assistance at the public expense is afforded in 36.7 %. As in the case of the Stockholm material, it is remarkable that the Poor Relief relatively seldom reports the alcoholics they help. The dangerous alcoholics comprise nearly a fourth of the material. The criminality figure is high. A fourth of the cases have been convicted for crimes. This figure is somewhat lower than that of the Stockholm material.

## Results.

It has been shown that in Malmö among men living up to the age of 75 years a little more than 14 per cent are taken care of at least once because of their being alcoholics of a chronic type. For women the corresponding figure is 0.5 per cent. The risk of being taken care of is about the same for persons born in Malmö as for persons immigrated to Malmö. These figures show that the spread of alcoholism is far greater than generally believed.

It has further been shown that alcoholics are reported again to a very large extent. 80 per cent are reported a second time. The figures are highest for those who were only warned after the first report and a little lower for those who were supervised for some time. The lowest frequency is found for alcoholics who were interned. The harder the measure taken, the greater is — as a rule — the success.

An investigation into the social character of the alcoholics has shown that principally people belonging to the poor classes are taken care of by official institutions, which is to be expected, as rich people are taken care of privately. It is further shown that the alcoholics to a large extent are socially degraded people, living on poor relief help or other public assistance. The criminality figure is high.

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# Über den normalen Vitamin A-Blutspiegel.

Von

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(Bei der Redaktion am 7. April 1942 eingegangen).

## Einführung.

Trotz vielen Untersuchungen die über den normalen Vitamin A-Gehalt des Blutes vorgenommen worden sind, kann man im neuesten Schrifttum öfters finden dass die Ergebnisse dieser Arbeiten nicht mit einander in Übereinstimmung sind und dass der Wert des normalen Vitamin A-Spiegels des Blutes daher noch immer nicht genügend bekannt ist. (30, 31, 38, 42, 49). Die Autoren schreiben dies nicht nur zu an Rassen-, Alters- und Gesundheitsunterschieden, vor allem sehen sie die auseinandergehenden Resultate als Folge der Unterschiede in der angewandten Methode. Zweifelsohne werden auch die Ernährungsgewohnheiten der Gegend wo die Untersuchungen vorgenommen wurden und der Wohlstand solch einer Gegend zur Zeit der Untersuchung einen gewissen Einfluss auf die Ergebnisse gehabt haben, weil der Vitamin A-Blutspiegel schliesslich von alimentären Einflüssen nicht unabhängig ist.

Untersuchungen über den normalen Karotingehalt des Blutes (5, 6, 19, 48) haben für die Kenntnis des normalen Vitamin A-Spiegels nur historischen Wert; der Gehalt an Provitamin A ist bekanntlich eine sehr wechselnde Grösse, weil sie unmittelbar alimentär bedingt ist, (5, 6) und daher mit den alltäglichen Nahrungsunterschieden bedeutend wechselt. Auch aus Ergebnissen von Untersuchungen bei welchen Vitamin A und Karotin zusammen be-

stimmt wurden (1, 2, 3, 13) ist es daher nicht möglich Schlussfolgerungen über den normalen Vitamin A-Gehalt zu ziehen.

Dass auch in Arbeiten bei denen beide Stoffe einzeln bestimmt wurden solche auseinandergehende Werte für das Vitamin A gefunden wurden ist als Folge der verschiedenen angewandten Bestimmungsmethoden anzusehen (38). Wenn ich aber die Resultate der Untersuchungen bei denen die bekannte von van Eekelen und Emmerie (9) angegebene Methode benutzt wurde, vergleiche, kommen auch aus diesen in vielen Ländern ausgeführten Arbeiten, bei denen die Autoren vielfach noch Änderungen in der Bestimmungsmethode angebracht haben, wohl sehr verschiedene Zahlen heraus, auch wenn diese Zahlen in die gleichen Einheiten umgerechnet werden. (18, 22, 23, 24, 31, 36, 38, 40, 41, 42, 43, 44, 45).

Es kann dann auch nicht wundernehmen dass man den Wert der Vitamin A-Bestimmung im Blut in Zweifel gezogen hat. Dazu kommt noch dass man vor kurzem meinte dass der Vitamin A-Gehalt eine Abspiegelung der Leberreserven sei, eine Voraussetzung die neuerdings auch bezweifelt wird. (30, 46).

Trotz dieser wenig ermunternden Übersicht bin ich der Meinung dass den vielen im Schrifttum niedergelegten Zahlen betreffs des Vitamin A-Gehaltes des Blutes einen Wert beigemessen werden kann und dass die Vitamin A-Bestimmung im Blute gewiss eine brauchbare Untersuchungsmethode ist. Diese Auffassung stützt sich auf den folgenden Tatsachen:

1) In der einzelnen Untersuchung sind die Resultate sehr wohl vergleichbar und solche Einzelarbeiten sind es dann auch die mehrere brauchbare Schlussfolgerungen ermöglicht haben.

2) In mehreren Untersuchungen konnte dargelegt werden dass der Vitamin A-Blutspiegel beim einzelnen Individuum einen relativ konstanten Wert darstellt. (4, 41, 45).

3) Aus der Literatur bekommt man den Eindruck dass der Vitamin A-Gehalt bei verschiedenen Personen sich mehr gleicht jeh mehr die verschiedenen Umstände wie Ernährung, Geschlecht, Alter, Jahreszeit und Arbeit gleich sind (32, 41, 45), eine Auffassung die ich in früherer Arbeit auch bestätigen konnte. (35).

Am besten zu übersehen ist die niederländische Arbeit auf diesem Gebiet, welche meistens verrichtet wurde von Untersuchern die im Hygienischen Laboratorium zu Utrecht die Methode zur

Bestimmung des Vitamin A-Gehaltes im Blutserum lernten die dort gefunden und ausgearbeitet wurde und auch sonst im Lande für mehrere Untersuchungen benutzt wurde. Die Resultate dieser Arbeit, die zum Teile in den Niederländen selbst (7, 8, 9, 10, 11, 12, 25, 26, 27, 28, 29, 50, 51, 52), zum Teile in den Niederländischen Ost-Indien (15, 16, 37) stattfanden zeigten, obwohl das Material bisweilen ziemlich heterogen war, wegen der Anwendung der gleichen Methode so viel Gleichförmigkeit dass sie Wolff veranlassten zur Abfassung des bekannten Schema:

| | | | | | |
|---|---|---|---|---|---|
| 0—4 | I. E. | pro | $cm^3$ | Serum: | schlecht |
| 4—8 | I. E. | » | » | » | mässig |
| mehr als 8 | I. E. | » | » | » | gut. |

Dieses Schema wurde von verschiedenen Autoren (16, 17, 21, 47) und auch von mir selber (33, 34) benutzt zum vergleichen gefundener Werte.

## Welcher Vitamin A-Gehalt ist als erniedrigt anzusehen.

Wolff nahm an dass die Grenze zwischen mässigem und ungenügendem Vitamin A-Gehalt des Blutes lag bei 4 internationalen Einheiten (I. E.). Weil eine genaue Begründung für diese Annahme in seinen Schriften fehlt ist es verständlich dass man die Richtigkeit dieser Grenze bezweifelt hat (23) auch dass man, so bald die Messung der Dunkeladaptation bekannt wurde, hoffte auf Untersuchungen in welchen die Dunkeladaptation und der Vitamin A-Gehalt des Blutes zugleicherzeit bestimmt werden konnten. In dieser Weise nämlich könnte man feststellen bei welcher Höhe des Vitamin A-Blutspiegels gestörte Adaptation auftritt, und könnte somit ausgemacht werden ob die bisher angenommene Grenze zwischen mässig und schlecht sich bewährte.

Solche Untersuchungen blieben nicht lange aus. Neben den Untersuchungen von Juhász-Schäffer (18) und von Pies und Wendt (31), die keine weitgehende Schlussfolgerungen zulassen, erschien die bekannte schwedische Arbeit von Lindqvist (23).

In dieser genauen und grosszügigen Untersuchung kommt Lindqvist auf Grund von Adaptationsmessungen zu der Folgerung dass die Grenze zwischen genügendem und ungenügendem Vitamin

A-Gehalt des Blutes liegt bei 7 I. E. Weil die von Wolff und Lindqvist gefolgte Methode die gleiche war hat das Resultat von Lindqvist's Untersuchungen ziemlich viel Aufsehen erregt. Bisher hat man diesen grossen Unterschied nicht anders als aus der Verschiedenheit der Ernährungsgewohnheiten in Schweden und den Niederländen zu erklären gewusst (46).

Lindqvist aber verglich die von ihm gefundenen Blauwerte mit »Vogan». Er führte seine Bestimmungen aus in einem Stufenphotometer und er nahm dabei die für »Vogan» angegebene Stärke als richtig an. Mittlerweile zeigte es sich schon aus einer Mitteilung (14) aus dem Laboratorium der Fabrik wo das »Vogan» angefertigt wird dass diese Angabe von 120,000 I. E. sehr anfechtbar ist.

Ein Teil des Vitamin A in »Vogan» kommt in veresterter Form vor. Diese besitzt eine grössere Vitamin A-Wirksamkeit als der daraus mittels Verseifung gewonnene Alkohol. Es zeigte sich dann auch dass die Zahl der I. E. welche man für »Vogan» findet abhängig ist von der Bestimmungsmethode, wobei hauptsächlich die biologische Methode grosse Unterschiede gegenüber den chemischen und physischen Bestimmungsmethoden zu sehen gab.

Deshalb war es ein guter Gedanke von Dr. J. P. K. van der Steur, den Blauwert von »Vogan» zum bestimmen. Dr. van der Steur erlaubte mir mitzuteilen dass er als Blauwert von »Vogan» höchstens 12,000 Lovibond Einheiten Blau (L. E. B.) fand. Durch diese Tatsache erscheint diese Frage plötzlich in ganz anderem Licht.

Wenn man für »Vogan» die Stärke von 120,000 I. E. pro $cm^3$ annimmt, stimmt also 1 L. E. B. in dieser Flüssigkeit überein mit 10 I. E. Wolff aber nahm immer den Umrechnungsfaktor 6.4 an, in dem Sinne dass 1 L. E. B. = 6.4 I. E.

Wenn man die Ergebnisse von Lindqvist in Einklang bringen will mit denen von Wolff, so muss man seine Zahlen multiplizieren mit $\frac{6.4}{10} = 0.64$. Die von Lindqvist angegebene Grenze von genügendem und ungenügendem Vitamin A-Gehalt des Blutes wird dann $7 \times 0.64 = 4.5$ I. E.

Wenn man diese Umrechnung anwendet, stimmen also die von Lindqvist und Wolff gefundenen Zahlen sehr wohl überein.

Ich bin deshalb der Meinung dass man mit Bestimmtheit sagen darf dass die damals von Wolff angenommene Grenze zwischen genügendem und ungenügendem Vitamin A-Gehalt des Blutserums bei 4 I. E. pro 10 $cm^3$ Serum als richtig betrachtet werden kann.

## Welcher Vitamin A-Gehalt muss als normal angesehen werden.

Im bisher in den Niederländen gebrauchten Schema wurde ein Vitamin A-Gehalt von 4—8 I. E. pro 10 cm³ Serum als »mässig» angesehen und erst ein Gehalt von mehr als 8 I. E. als »gut». Bei gesunden Personen findet man regelmässig Werte die unter 8 I. E. liegen und es fragt sich deshalb ob alle diese Personen eigentlich

**Tabelle I.**

| | Herbst | | | | Frühjahr | | | |
|---|---|---|---|---|---|---|---|---|
| | Vitamin A[1] | | Karotinoide[2] | | Vitamin A[1] | | Karotinoide[2] | |
| | Mann | Weib | Mann | Weib | Mann | Weib | Mann | Weib |
| Vitaminisierte Margarine | 7.4 | 4.4 | 6.7 | 6.0 | 5.7 | 6.9 | 3.3 | 3.3 |
| | 7.3 | 6.2 | 9.0 | 5.4 | 6.5 | 7.2 | 5.8 | 6.6 |
| | 6.2 | 6.5 | 9.6 | 5.4 | 6.4 | 7.6 | 4.0 | 3.9 |
| | 5.4 | 4.7 | 8.6 | 4.0 | 7.7 | 4.7 | 3.1 | 2.5 |
| | 6.1 | 5.2 | 6.7 | 7.4 | 4.1 | 4.4 | 2.9 | 2.6 |
| | 5.1 | 5.2 | 3.3 | 7.6 | 6.0 | 5.7 | 3.9 | 4.5 |
| | 5.7 | 5.2 | 4.0 | 7.3 | 6.0 | 5.9 | 5.0 | 9.3 |
| | 7.3 | 6.0 | 4.5 | 5.6 | 5.6 | 7.2 | 5.3 | 3.8 |
| | 7.2 | 5.6 | 6.9 | 9.5 | 6.9 | 7.3 | 5.8 | 5.3 |
| | 4.6 | 4.2 | 4.1 | 5.6 | 5.4 | 7.4 | 2.1 | 4.3 |
| | 5.1 | 6.2 | 5.4 | 6.3 | 7.1 | 6.5 | 5.8 | 6.8 |
| | 5.0 | 5.5 | 5.9 | 4.7 | 6.9 | 6.3 | 3.2 | 4.1 |
| | | | | | 6.1 | 6.0 | 6.9 | 3.5 |
| | | | | | 6.2 | 5.4 | 5.7 | 4.2 |
| Mittel | 6.0 | 5.4 | 6.3 | 6.2 | 6.2 | 6.3 | 4.5 | 4.6 |
| Nicht vitaminisierte Margarine | 5.0 | 5.7 | 7.4 | 6.7 | 5.6 | 6.2 | 2.6 | 4.1 |
| | 5.4 | 5.4 | 4.4 | 5.4 | 5.6 | 2.7 | 4.7 | 3.5 |
| | 4.5 | 2.7 | 4.1 | 5.3 | 5.6 | 6.2 | 2.8 | 4.1 |
| | 6.4 | 6.1 | 13.6 | 14.9 | 6.1 | 6.2 | 6.2 | 4.7 |
| | 6.7 | 4.3 | 9.1 | 7.1 | | | | |
| | 7.2 | 4.3 | 3.4 | 8.9 | | | | |
| | 6.4 | 6.0 | 10.2 | 8.2 | | | | |
| Mittel | 5.9 | 4.9 | 7.5 | 8.2 | 5.7 | 5.3 | 4.0 | 4.1 |
| Sahnenbutter | 9.0 | 6.2 | 8.9 | 12.9 | 7.9 | 6.6 | 16.4 | 10.8 |

[1] In I. E. pro 10 cm³ Serum.
[2] In $\gamma$ pro 10 cm³ Serum.

Wohlhabenden gewählt, was aber nicht richtig sein kann. Im Allgemeinen soll man sich ja nicht richten nach Wahrnehmungen bei Wohlhabenden wenn man sucht nach einem Wert der für »genügend» gehalten werden kann.

In einer eigenen Untersuchung meine ich bewiesen zu haben dass schon ein Vitamin A-Gehalt unter 8 I. E. als genügend anzusehen ist. Die Zahlen stammen von einer Untersuchung die ursprünglich nur zum Ziel hatte den Einfluss der Jahreszeit auf das Vitamin A zu erforschen. (35). Es wurden hierzu 5 gesunde Ehepaare untersucht am Beginn (Ende Februar, Anfang März) und am Ende (zweite Hälfte April) des »biologischen Frühjahrs». Die Anforderungen an die zu untersuchenden Personen und der Gang der Untersuchung waren die gleiche als oben beschrieben. Nur bei einem Ehepaar war die Nahrung von Mann und Weib ungleich. Eigentlich wurde bei dieser Untersuchung eine sehr physiologische Belastungsprobe ausgeführt. Die Ergebnisse sind folgende:

*Ehepaar A.*

Nahrungsaufnahme von Mann und Weib: gleich.

Ernährungsumstände in den verschiedenen Zeitpunkten der Bestimmung: gleich.

Gebrauchte Butterart: vitaminisiertes Margarin.

**Tabelle II.**

| | 20 Februar | | 15 April | | Anstieg | |
|---|---|---|---|---|---|---|
| | Mann | Weib | Mann | Weib | Mann | Weib |
| Vitamin A in I. E. ..... | 4.1 | 4.4 | 6.6 | 5.3 | +2.5 | +0.9 |
| Karotinoide in $\gamma$. ..... | 2.9 | 2.6 | 4.4 | 4.6 | +1.5 | +2.0 |

Der Vitamin A-Gehalt ist bei Mann und Weib gestiegen, beim Manne sogar 2.5 I. E. Der Anstieg des Vitamin A-Gehalts beim Manne ist grösser als beim Weibe. Der Karotingehalt hat bei Mann und Weib zugenommen. Bei den Karotinoiden ist der Spiegel beim Manne weniger gestiegen als beim Weibe.

*Ehepaar B.*

Nahrungsaufnahme von Mann und Weib: gleich.

Ernährungsumstände in den verschiedenen Zeitpunkten der Bestimmung: gleich.

Gebrauchte Butterart: vitaminisiertes Margarin.

Tabelle III.

| | 14 März | | 15 April | | Anstieg | |
|---|---|---|---|---|---|---|
| | Mann | Weib | Mann | Weib | Mann | Weib |
| Vitamin A in I. E. ..... | 6.2 | 5.4 | 7.3 | 5.9 | +1.1 | +0.5 |
| Karotinoide in γ. ..... | 5.7 | 4.2 | 6.2 | 5.2 | +0.5 | +1.0 |

Der Vitamin A-Gehalt hat bei Mann und Weib zugenommen. Beim Manne ist der Anstieg höher als beim Weibe. Bei diesem Ehepaar gibt es ein geringerer Anstieg als beim Ehepaar aus Tabelle II. Der Vitamin A-Gehalt war hier auch weniger tief als beim genannten Ehepaar. Die anzufüllenden Defizite waren anscheinend geringer. Der Karotingehalt ist bei Mann und Weib gestiegen. Bei den Karotinoiden ist der Anstieg beim Manne geringer als beim Weibe.

*Ehepaar C.*

Nahrungsaufnahme von Mann und Weib: gleich.

Ernährungsumstände in den verschiedenen Zeitpunkten der Bestimmung: gleich.

Gebrauchte Butterart: vitaminisiertes Margarin.

Tabelle IV.

| | 13 Februar | | 19 April | | Anstieg | |
|---|---|---|---|---|---|---|
| | Mann | Weib | Mann | Weib | Mann | Weib |
| Vitamin A in I. E. ..... | 6.5 | 7.2 | 6.6 | 6.2 | +0.1 | —1.0 |
| Karotinoide in γ. ..... | 5.8 | 6.6 | 5.9 | 9.2 | +0.1 | +2.6 |

Der Vitamin A-Gehalt ist beim Mann praktisch gleich geblieben. Beim Weibe hat er 1 I. E. abgenommen. Bei diesem Ehepaar war der Vitamin A-Gehalt am Ende des Winters wieder höher als bei den oben beschriebenen Ehepaaren. Ein Anstieg im »biologischen Frühjahr» tritt nicht auf. Vielleicht war der Vitamin A-Gehalt des Blutes in diesem Falle genügend hoch und soll die Abnahme beim Weibe gesehen werden als eine natürliche Schwankung (nach unten) eines normalen Vitamin A-Gehaltes. Hieraus würde man schliessen können dass ein Vitamin A-Gehalt von 6 bis 7 I. E. offenbar genügend hoch ist.

Der Karotinoidengehalt hat bei Mann und Weib zugenommen. Bei den Karotinoiden ist der Spiegel beim Manne weniger gestiegen als beim Weibe.

*Ehepaar D.*

Nahrungsaufnahme von Mann und Weib: gleich.

Ernährungsumstände in den verschiedenen Zeitpunkten der Bestimmung: ungleich.

Wo die Familie bei der ersten Bestimmung nicht-vitaminisiertes Margarin gebrauchte, gebraucht sie jetzt da der Mann arbeitslos geworden ist das an arbeitslosen verabreichte vitaminisierte Margarin.

Gebrauchte Butterart: wie oben beschrieben.

**Tabelle V.**

| | 26 Februar | | 17 April | | Anstieg | |
|---|---|---|---|---|---|---|
| | Mann | Weib | Mann | Weib | Mann | Weib |
| Vitamin A in I. E. ..... | 5.6 | 2.7 | 6.1 | 4.6 | +0.5 | +1.9 |
| Karotinoide in $\gamma$. ..... | 4.7 | 3.5 | 5.3 | 7.1 | +0.6 | +3.9 |

Der Vitamin A-Gehalt hat bei Mann und Weib zugenommen. In diesem Falle ist der Anstieg beim Manne aber kleiner als beim Weibe. Der Mann steigt nur 0.5 I. E. bei dem ziemlich guten Ausgangswert von 5.6 I. E.; das Weib aber hat ein grosses Defizit zu ergänzen. Ihr Vitamin A-Gehalt des Blutes am Anfang des biologischen Frühjahrs ist einer der niedrigsten von mir beobachteten Werte. Die mit dem vitaminisierten Margarin zugeführte Menge von Vitamin A verursacht bei ihr im Blute einen Anstieg von 1.9 I. E.

Der Karotinoidengehalt hat bei Mann und Weib zugenommen. Beim Manne ist der Anstieg bedeutend geringer, obwohl die Ausgangswerte nicht solch einen grossen Unterschied zeigten.

*Ehepaar E.*

Nahrungsaufnahme von Mann und Weib: ungleich.

Die arbeitslose Familie gebrauchte das an Arbeitslosen verabreichte vitaminisierte Margarin. Die Frau aber gebrauchte für sich allein ein halbes Pfund Sahnenbutter in vierzehn Tagen.

Ernährungsumstände in den verschiedenen Zeitpunkten der Bestimmung: ungleich.

Gebrauchte Butterart: wie oben beschrieben.

Tabelle VI.

| | 22 Februar | | 17 April | | Anstieg | |
|---|---|---|---|---|---|---|
| | Mann | Weib | Mann | Weib | Mann | Weib |
| Vitamin A in I. E. ..... | 3.5 | 9.5 | 5.8 | 9.2 | +2.3 | —0.3 |
| Karotinoide in γ. ..... | 3.5 | 8.4 | 5.5 | 10.8 | +2.0 | +2.4 |

Der Vitamin A-Gehalt hat beim Manne zugenommen, beim Weibe etwas abgenommen. Der Mann hat offenbar mit einem Ausgangswert von 3.5 I. E. ein grosses Defizit zu ergänzen und steigt unter fortwährendem Gebrauch von vitaminisiertem Margarin 2.3 I. E. Die Frau hat unter Gebrauch von Sahnenbutter einen sehr hohen Vitamin A-Gehalt des Blutes, wie der auch bei den Sahnenbutter gebrauchenden Ehepaaren die in Tabelle I aufgenommen sind gefunden wurde. Ich meine die beiden Werte beim Weibe so auffassen zu müssen dass man sagen kann dass sie bei beiden Bestimmungen einen sehr hohen Vitamin A-Gehalt des Blutes hatte.

Der Karotingehalt hat bei Mann und Weib zugenommen. Bei den Karotinoiden ist der Spiegel beim Manne weniger gestiegen als beim Weibe, obwohl die Ungleichkeit der gebrauchten Butterart in diesem Falle keine Vergleichung zulässt. Der Gehalt an Karotinoiden beim Weibe ist bei beiden Bestimmungen hoch, wie das auch bei den Sahnenbutter essenden Ehepaaren aus Tabelle I gefunden wurde.

Es stellt sich also heraus dass ein Vitamin A-Gehalt von 6—7 I. E. unter der physiologischen Belastung des Frühjahrs nicht ansteigt. Dass in allen Fällen wirklich von einer Belastung gesprochen werden kann ist deutlich zu sehen aus der Zunahme des Karotinspiegels der bei allen Personen gefunden wurde. Ein Vitamin A-Gehalt von 6 bis 7 I. E. darf also als genügend aufgefasst werden.

## Zusammenfassung.

Unter 4 I. E. pro 10 cm³ Blutserum soll der Vitamin A-Gehalt des Blutes als zu niedrig aufgefasst werden. Ein genügender Vitamin A-Gehalt liegt bei 6 bis 7 I. E.

Unter gewissen besonderen Bedingungen können höhere Werte beobachtet werden.

## Schrifttum.

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# Clinical Investigations About Complement.

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## *I. Estimation of the complement-action and of the anti-complementary power of serum.*

Most investigators who have been engaged in the estimation of the complement-action of serum use the method which might be called »complement titration». In the monograph which Osborn (1) has devoted to complement, we therefore find that this »serial tube» method is called the classic and generally used method. The number of varieties in putting this method into practice is very large, on account of which comparison of the results often meets with difficulties.

As, in what follows, a comparison between this »complement titration» and another method to measure the complementary power of serum will be spoken of, we shall first give a short description of the technique of which we availed ourselves up till now.

*Technique of the »complement titration»* (»serial tube» method). In a series of 8 small tubes equal quantities, in our experiments mostly 0.1 $cm^3$, normal saline are introduced. To the first tube we add 0.1 $cm^3$ of the serum to be examined. After having mixed it well with the saline, 0.1 $cm^3$ of this mixture is put into the next tube. After having mixed the contents of this tube, again 0.1 $cm^3$ of this mixture is put into the next tube. Continuing in this way we get a series of

dilutions of serum in normal saline, whilst the quantity of liquid is the same in all the test-tubes. The dilution of the serum in the first tube is ½, that in the second ¼ and in the next 1/8, 1/16, 1/32, 1/64, 1/128 and 1/256 respectively. Now 0.1 cm³ 5 % suspension of washed red corpuscles of a sheep and 0.1 cm³ amboceptor dilution (one drop of rabbit serum with an amboceptor-titer of 1/3000 is added to 20 cm³ normal saline) is introduced in each tube. At last 0.1 cm³ saline is added to each of the tubes. After shaking, the tubes are placed in a water-bath of 37° C for half an hour and then put aside for a couple of hours. The reading off is as follows: the tubes in which complete haemolysis has taken place are marked with three crosses, those in which strong, but not complete haemolysis is to be seen with two and those in which haemolysis is only weak with one cross. In this way the serum dilution is established by which still complete haemolysis takes place and that by which haemolysis can still only just be seen. Last-mentioned dilution we called »complement titer».

It struck us that the titration with serum obtained from healthy and sick people produced almost the same results, a fact already pointed out by many research-workers. Yet small differences were found, to which, however, we did not dare to attach any value. For the decision wether there is still just a slight sediment of red cells in the tube or not depends slightly on the research-worker. The same may be said concerning the decision about the colour of the supernatand fluid. And if we finally realise that the difference of one tube by the reading-off results in a great difference in outcome, then it is obvious that we are looking for, if possible, a more accurate and yet simple method, to measure the complementary power.

Indeed many attempts have been made in that direction. Most of these are based on the accurate estimation of the quantity of haemoglobin which through the action of a fixed quantity of serum can be liberated from erythrocytes. The results obtained in this way were more accurate, it is true, but the method usually did not gain in simplicity.

As well as by measuring the liberated quantity of haemoglobin it must be possible to obtain a measure for the complementary power by measuring the quantity of erythrocytes which is haemolysed. So far as we have been able to ascertain this principle has up till now only been used by Meerseman and Perrot (2).

The method as we have applied it is as follows (3). We use the haematocrit. These consists of a capillary which is closed at the bottom and which at the top passes into a funnel-shaped dilatation. (fig. 1). The capillary part has a volume of 0.05 cm³ and is accurately subdivised into 100 parts. By means of a pipette 0.1 cm³ of the serum to be examined is put into the wide part of the haematocrit. To this is added 0.7 cm³ of a 5 % suspension (in normal saline) of washed sheep's corpuscles, after care has been taken that by means of repeated shaking this suspension is perfectly homogene-

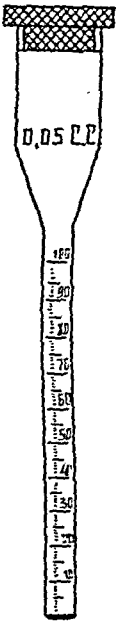



FIG. 1 HAEMATOCRIT

ous. Finally an excess of an amboceptor solution, in our experiments this was 0.1 cm³, is added. This solution consisted of 20 cm³ of normal saline to which was added one drop of amboceptor-containing rabbit's serum (titer about 1/3000). In another haematocrit is put 0.1 cm³ serum which by means of heating for half an hour at 56° C. has been inactivated, besides exactly the same quantity of suspension of red cells and amboceptor. After mixing, both haematocrits are closed by means of a fitting stopper and placed into a water-bath of 37° C for half an hour. After that they are whirled at a speed of 3000 rotations in a minute. Spinning is continued till further whirling no longer results in a decrease of the height of the

column of cells. We achieved this with a »Corda» centrifuge in half an hour. The height of the column of cells can always be read off very accurately. By subtracting the height of the column in the first haematocrit from that in the second, (control-tube) in which there is inactivated serum, one knows the volume of cells which have been haemolysed by 0.1 $cm^3$ serum.

One must make sure that there was enough amboceptor on hand at the experiment by ascertaining whether the addition of a more concentrated amboceptor-solution, does not bring on other results.

We have found that the reliability of this method is sufficient. With the same serum exactly the same figures were repeatedly found, at other times small differences were found. The biggest mistake did not amount to more than 10 %. The reading off of the height of the column of cells is easily possible to an exactitude of one haematocrit-grade. The presence of ghosts had no disturbing influence on the reading off. The method does not take much time, so that it is possible to do a great number of complement-estimations in a short time, whilst, if the same suspension of red cells is used one control-tube for all the tests is sufficient. The required quantity of serum is slight. With 20 drops of blood from a finger even a measuring in duplicate can be made at which a blood-sugar pipette of 0.1 $cm^3$ can very well be used. It may be desirable for experimental purposes to probe coloured fluids. By using the haematocrit-method this is possible without any objection.

In order to be able to compare the results obtained by this haematocrit-method with those of the »complement titration» we asked ourselves: *what influence has the dilution of serum on the complement-action*? This influence we tried to trace as follows.

In a number of haematocrits a falling quantity of serum was put in such a way that the first haematocrit contains 0.2 $cm^3$ serum and the next 0.15 $cm^3$, 0.1 $cm^3$, 0.06 $cm^3$, 0.04 $cm^3$, 0.02 $cm^3$ respectively and the last 0.01 $cm^3$. The total quantity of liquid present in each haematocrit was made equal by supplementing to 0.2 $cm^3$ with normal saline. To the first haematocrit no saline was introduced, to the second 0.05 $cm^3$ etc. Next 0.7 $cm^3$ 5 % suspension of sheep's erythrocytes and 0.1 $cm^3$ amboceptor-solution was introduced to each haematocrit. Besides two haematocrits were got ready of which the one contained 0.2 $cm^3$ of inactivated serum and the other the same quantity of normal saline (control tubes).

Also to this tubes the above mentioned quantity of red cells and amboceptor-solution is introduced. All the tubes were put aside for half an hour at 37° C and then whirled. So we have made a series of serum dilutions of which the serum concentrations are more or less comparable with those of the complement-titration. The first tube contains 20 % serum, the last 1 %. The complement-action in each tube may be found by subtracting the height of the column of cells from that of the control-tubes in which there is the saline or inactivated serum.

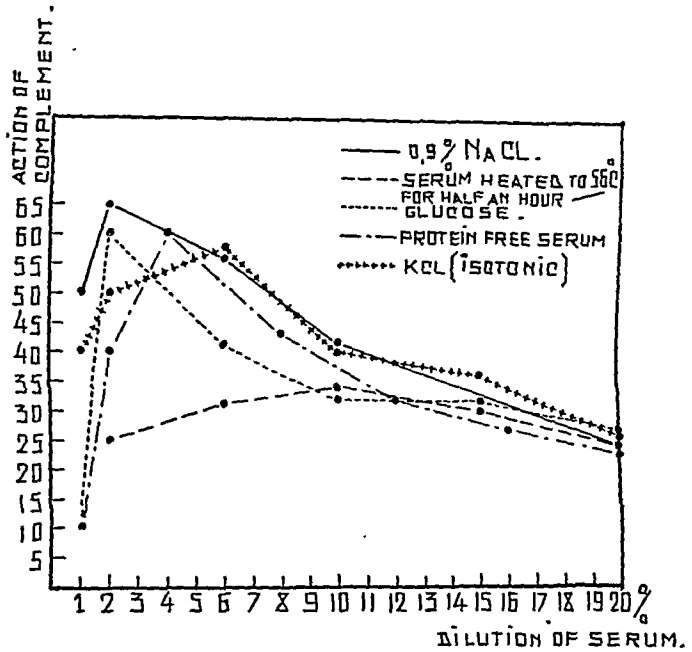



FIG. 2 RELATION BETWEEN COMPLEMENT-ACTION AND DILUTION.

We have calculated the activity of the complement by various dilutions by deducing from the figures found how the action of 0.1 $cm^3$ of serum by the various dilutions would have been. In this way it could be ascertained that the activity of the complement is greatly dependent on the dilution and indeed in such a way that it increases to a certain dilution in proportion to the degree of the dilution. The result of this is that the activity in the tubes in which there is 2 % serum is 100 % to 200 % higher than in those in which there is 20 %. A distinct drop of the activity is to be seen in the tubes containing 1 % serum (see fig. 2). There is, as it were, a critical point. This is not always found by the same dilution.

*On the ground of these experiences estimation of complement based on the making of serum-dilutions*, as is the case with the »complement-titration» (»serial tube» method) *cannot be called exact*. For in making dilutions not only the quantity of serum to be examined changes, but also the dilution and therefore the activity of this serum.

That this remark is indeed of practical importance appears from the following experiment. With two sera of which through the

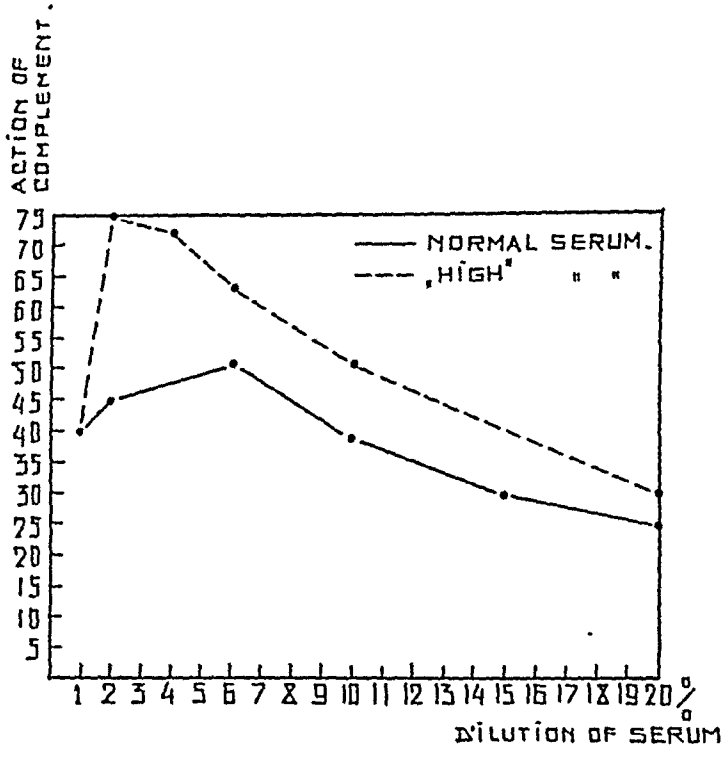



FIG. 5. RELATION BETWEEN COMPLEMENT-ACTION AND DILUTION WITH 0,9% NACL OF NORMAL AND "HIGH" SERUM.

haematocrit-method it was known that one had a normal, the other a high complementary power a »complement titration» was performed. Indeed there was a difference to be seen between the two sera. This consisted in the fact that the normal serum at a dilution of 1/64 only showed a trace of haemolysis, whereas the »strong» serum at that dilution showed a somewhat stronger haemolysis. Of both sera a dilution-series was made in haematocrits in the manner described above. By means of the results obtained we again calculated the activity at various dilutions. Both the »strong»

serum and the normal showed up to a certain point a stronger activity at increasing dilution. The maximum activity of both the sera was about twice as great as at a dilution of 20 %. Both the »strong» and the normal serum showed in all the dilutions (i. e. to 1 %) haemolysis (see fig. 3).

It must be remarked that when the haematocrit-method for the estimation of the complementary power of serum is applied, it is advisable always to use the same quantity of sheep's erythrocytes. For if a varying quantity of red cells is added to an equal quantity e. g. 0.05 cm³ of

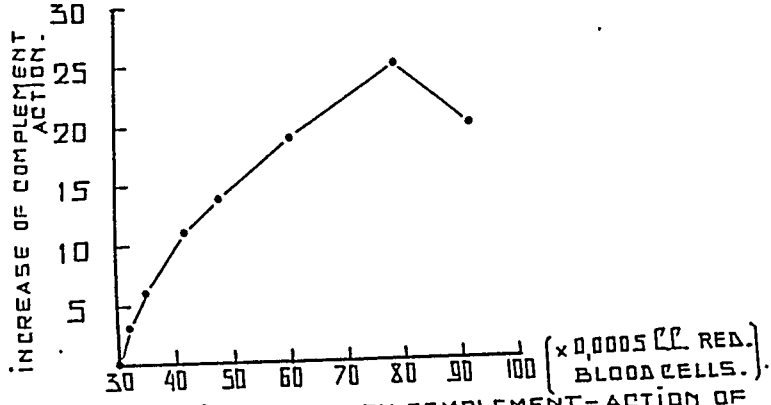



FIG. 4 RELATION BETWEEN COMPLEMENT-ACTION OF 0.05 C.C. NORMAL SERUM AND NUMBER OF RED CELLS.

normal fresh serum, taking care that the dilution of the tested serum is the same in all the tubes, then the result is as follows (see fig. 4). *The more erythrocytes are present in the tube the more are haemolysed by 0.05 cm³ of serum.* If the quantity of cells added to 0.05 cm³ of serum was e. g. 78 grades (i. e. 0.039 cm³) then about 80 % more cells were haemolysed by this serum than in a haematocrit in which there had originally been only 30 grades (0.015 cm³) red cells. Not all the tested sheep's erythrocytes showed an equally distinct rise as is indicated in fig. 4, but an increase of the complementary power of 40 or 50 % was very common. This implies that when following the haematocrit-method 10 grades more red cells are used than was prescribed, 10 % higher value may to be found.

To explain this phenomenon it seems to us plausible to assume that there are in a suspension more and less resistant red cells. The more cells there are now added to the test the larger the absolute quantity of cells will be which are little resistant against the action of complement. The complement on hand will then exclusively be used to haemolyse red cells which are little resistant, so that it is obvious to assume that the number of red cells which falls a victim to the complement is larger. By a certain proportion between the complement on hand and the quantity of red cells

all complement may be used for less resistant cells, so that if more red corpuscles are present no further increase is to be expected. This may be read off from our curve (fig. 4). For if more than 78 grades (0.039 $cm^3$) of red cells are present no further increase of complementary action is to be seen. In our opinion the method can be used to investigate the resistance of red cells in general, so also of human erythrocytes against the influence of complement. Experiments about this are still being made.

*By means of the above exposition we have tried to show that estimation of complement by means of the haematocrit-method, both on practical and theoretical grounds is to be preferred to methods by which use is made of dilutions of the serum to be tested.*

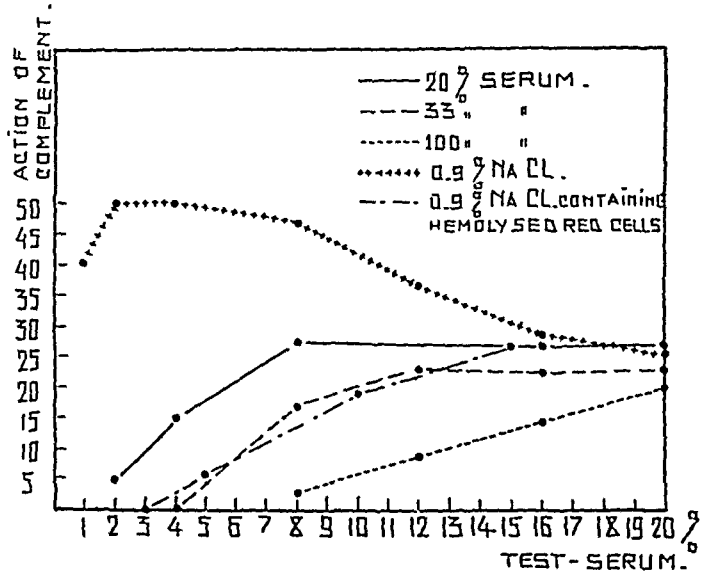



FIG. 5. INFLUENCE OF INACTIVATED (½ H. 56° C.) SERUM ON COMPLEMENT-ACTION.

The influence found of the dilution on the complementary action we subjected to a further investigation. Up till now normal saline was used as diluting liquid. It was a matter of course to investigate how other diluting liquids would behave. We therefore repeated the tests described with an isotonic potassium-chloride- and glycose-solution and with serum from which the proteins after precipitation are removed. All the grafics had the shape as described for saline (fig. 2). If we added however the same quantity of serum inactivated by heating (during half an hour at 56° C), then the grafic was flatter (fig. 2). Still flatter the grafic was if the total quantity of serum was increased and amounted e. g. to 33 % (fig. 5). Finally we took care that there was no saline at all in the tubes.

This we achieved by preparing both the red cells and the ambo-ceptor-dilution with inactivated serum. The curve obtained in this way was almost a straight line (fig. 5). So it is clear that inactivated serum has a checking influence on complement.

We compared sera with strong and with normal complementary action with each other as regards their checking qualities, but did not find any differences.

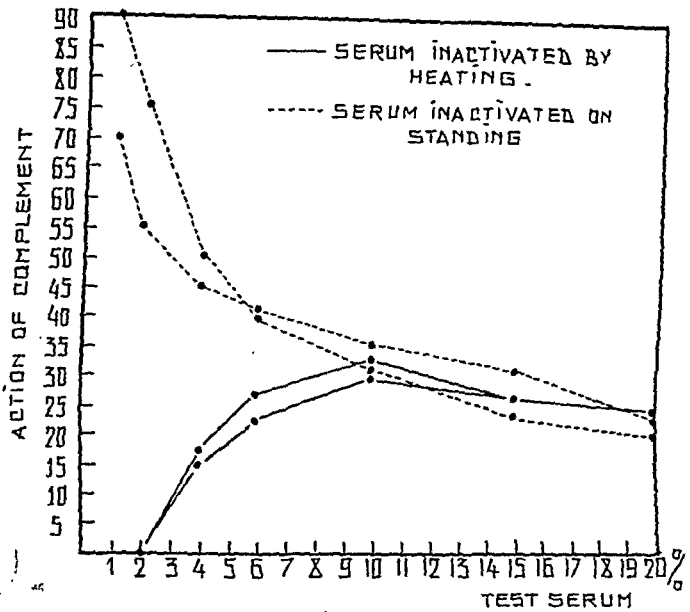



FIG. 6. DIFFERENCE BETWEEN ACTION OF SERUM INACTIVATED BY HEATING AND SERUM INACTIVATED ON STANDING UPON COMPLEMENT-ACTIVITY.

Quite different the results of the experiments became, if they were made with a serum of which the complement had become inactive by keeping it at room-temperature for a week. The grafic which now resulted rather resembled the one which had been seen with normal saline, potassium-chloride, glycose and serum from which the proteins after precipitation are removed. The activity of the complement in this fluid rose even higher at a greater dilution than in the before mentioned fluids. (see fig. 6) [1]. So it appears that the anti-complementary action of serum is a. o. dependent on the way in which it was inactivated.

[1] Not every serum which is kept in stock for some time behaves like the one mentioned above. After being kept at 17° C. some sera show a strong anti-complementary action which diminishes when for short time the temperature is raised to 56° C [see also Nattan-Larrier and Grinard (4)].

The question still remains whether besides the dilution there are other factors which are the cause that, when the dilution increases the complementary action, at least to a certain point, increase also. One of these causes, in our opinion, lies in an anti-complementary action of the contents of the erythrocytes liberated by means of haemolysis. In proportion as the dilution in our tests increases the concentration of it decreases. That the haemoglobin-containing liquid, which is obtained by haemolysing red cells really has a check-

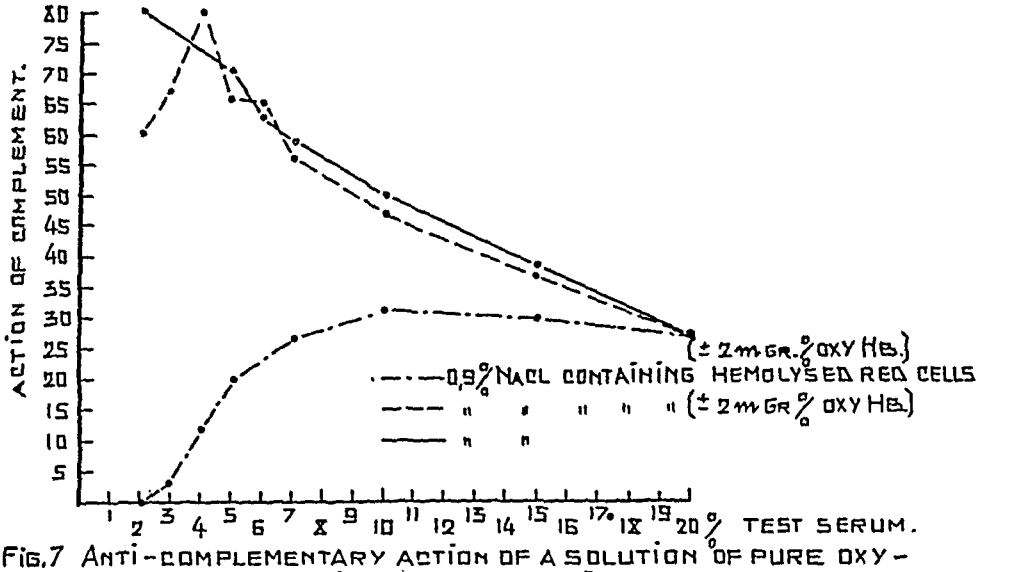



FIG. 7 ANTI-COMPLEMENTARY ACTION OF A SOLUTION OF PURE OXY-HEMOGLOBIN IN 0.9% NaCl AND OF 0.9% NaCl, CONTAINING HEMOLYSED RED CELLS.

ing influence on the complement can be proved by means of the following experiment.

Again we make the mentioned serum dilutions, but we now use normal saline in which there are haemolysed red cells. This was prepared by haemolysing sheep's erythrocytes through the addition of water. After centrifuging half the volume of 2.7 % saline was added to the supernatant liquid. The curve obtained with this liquid deviated entirely from that by which haemoglobin-free normal saline was used. In contrast to this the first-mentioned curve had almost a flat shape (fig. 5). The similarity of this grafic with that of serum which had been inactivated by heating is obvious, so that to this haemoglobin-containing liquid anti-complementary action may be ascribed. This explains in our opinion, at any rate partly, the influence which the dilution has on the complementary action.

To the haemoglobin itself no influence may be ascribed in this case. This appears from experiments at which the anti-complementary action of a solution of pure oxy-haemoglobin in normal saline is investigated. This action seems to be approximately similar to that of saline. As may be read off from fig. 7, these two liquids give in our experiment quite different curves from saline which contains, so many haemolysed red cells that the haemoglobin concentration is equal to that of the first-mentioned solution of pure haemoglobin.

*So the contents of red blood cells liberated by haemolysis have anti-complementary power, which may not be ascribed to the haemoglobin.*

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*It appears that the method described by us can be used for investigations concerning anti-complementary power of substances.*

In order to investigate *the anti-complementary action of normal sera* closer, we inactivated these sera at a temperature of 56° C. during a very short and also for a longer time. To be able to perform a large number of estimations in a short time it seemed advisable to simplify the method a little. We acted as follows. Into a haematocrit 0.04 $cm^3$ of normal fresh human serum was put of which the complementary action was known. To this was added 0.16 $cm^3$ of the liquid which was to be tested on her anti-complementary action and finally again 0.7 $cm^3$ 5 % suspension of sheep's erythrocytes in saline, besides 0.1 $cm^3$ of amboceptor-dilution.

To express in figures the anti-complementary action of a liquid to be investigated, one would have to know the action of 0.04 $cm^3$ of normal (test-)serum with and without the addition of the liquid to be investigated. As in both the experiments the same dilution of the test-serum must be present 0.16 $cm^3$ of a liquid without any anti-complementary action would have to be added when carrying out the control-test. Such a liquid is unknown to us. Now it has been proved that through the addition of sera with exceedingly slight anti-complementary action 0.04 $cm^3$ of normal serum can unfold at this dilution a complementary action which is almost as strong as the complementary action of 0.1 $cm^3$ of this test-serum in the dilution, as was customary by the complement estimation. In this way the complementary power of the test-serum is taken into account, whereas by comparative investigation the mistake, if any, remains the same in all experiments.

Let us assume that complementary action of a certain test-serum, used for this experiment amounts to 45. Of this serum 0.04 cm³ is put into a haematocrit. To this is added 0.16 cm³ of the liquid of which one wants to measure the anti-complementary

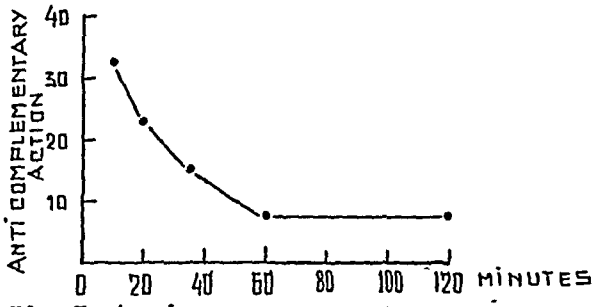



FIG. 8. ANTI-COMPLEMENTARY ACTION OF NORMAL SERUM HEATED TO 56° C FOR DIFFERENT TIMES

power. Finally one adds to it, by means of a pipette 0.7 cm³ 5 % suspension of sheep's erythrocytes and 0.1 cm³ of amboceptor-dilution. The mixture is put aside for half an hourr at 37° C. After centrifuging there appear to be 20 grades of red cells less in this

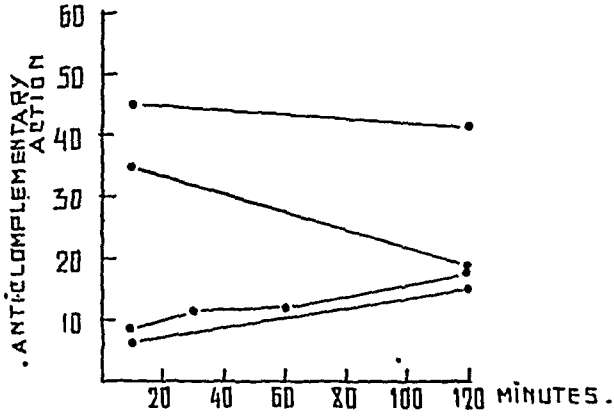



FIG. 9. ANTI-COMPLEMENTARY ACTION OF SERUM HEATED TO 56° C. FOR DIFFERENT TIME

haematocrit than in the control-tube [1], so that, when the liquid to be examined is present the complementary action of 0.04 cm³ of test-serum is only 20. According to what was said above the anti-complementary action of the investigated liquid is therefore 45—20, so 25.

[1] The control-tube contains 0.04 cm³ of inactivated serum instead of the test-serum, for the rest the same liquids.

In this way we examined numerous normal and pathological sera. With some sera it was evident that the duration of the inactivation at 56° C had its influence on the anti-complementary power of this serum. Figure 8 shows how the inactivation during 10.20 etc. minutes at 56° C changes the anti-complementary power of a normal serum. Not all sera give the same curves. Figure 9 shows some other curves. The cause of these differences is not clear to us. Neither has it appeared possible to draw conclusions from the shape of the curves which might be of interest to the clinic. But we do think that we may declare that there is no direct connection between the complementary power of a certain serum and its anti-complementary action. If a serum is found with slight complementary action, then this needs not imply at all that the anti-complementary power should be particularly great. Nor is the reverse true.

## Summary.

A comparative inquiry is made concerning two methods to estimate haemolytic complement in serum quantitavely. It appears that the method which was described as the haematocrit-method is on theoretical grounds to be preferred to methods by which serum dilutions (»serial-tube method») are used. The practical advantage of the haematocrit method to many others consists in this, that it is possible to perform a great number of estimations in a short time with slight resources. The quantity of serum necessary for one experiment is 0.1 $cm^3$. The method can also be used for coloured liquids.

To obtain comparable results with the haematocrit method it is advisable to follow the given instructions accurately. The activity of complement is dependent on the one side on the environment (strength of dilution and nature of diluting-liquid) in which the serum is investigated, on the other on the quantity of erythrocytes, present at the experiments. Within certain limits at any rate the rule holds good: the more erythrocytes there are present the stronger the complement-action is which is unfolded. This might be explained by assuming that there exist against complementary action more and less resistant red cells.

Not only for the estimation of the complementary power of serum, but also for measuring the anti-complementary power of liquids the haematocrit method can be applied.

II. *Information concerning estimation of complement in the clinic.*

By means of the haematocrit method described above, a great number of complement estimations was performed on healthy and sick people. By far the most of the investigated sera showed normal values, that is to say, that 0.1 $cm^3$ of serum is able to haemolyse under the mentioned circumstances 35—50 times 0.005 $cm^3$ of sheep's erythrocytes. Values between 35 and 50 we call normal. More estimations on the same person in the course of days and weeks taught that the complementary action in normal as well as in most of the sick people was liable to very slight fluctuations, a fact already pointed out innumerable times. Still a number of patients was found in which the complementary power was high (55—65) or very low (10—15), whilst in one patient no complement-action at all even could be proved to exist.

Repeatedly a rise or a fall of the complement could be observed during the course of the illness, at which a connection with the course of the illness was hard to deny. Yet I want to say only a few words as to the significance of the estimation of complement for the clinic, because the number of patients investigated is not yet sufficient to justify conclusions concerning it.

The opinion of Goldner, Bauer, Lipkin, Meerseman and Perrot (5) and others that with extensive damage of liver-tissue the complementary power of the serum is low, I have been able to confirm so far that in some patients with atrophic cirrhosis of the liver the complement was indeed low. It must be remarked however that repeatedly low figures also occur with other diseases, sothat one would only be allowed to say: *if in a patient with icterus the complementary power of the serum is found high, this is an argument telling against the existence of an atrophic cirrhosis.*

In some patients with Weil's disease (spirochaetal jaundice) and with catarrhal jaundice normal, sometimes even high values were found, whereas the complementary power of the serum of patients with metastatic tumors in the liver was sometimes a little too low, often normal however. Strikingly high figures (about 60) were repeatedly found in patients who were suffering from a mechanical obstruction of the bile-ducts through whatever cause (gall stones, tumors).

Besides it has struck me that in a number of patients with general diseases of the bones (Kahler's disease, Schüller-Christian's disease, Albers-Schönberg's disease, carcinomatosis) low, repeatedly even very low values (5—15) might be found. Observations taken on patients with local affections of the skeleton however (tuberculosis, tumor) showed us normal values.

Some patients suffering from lipoid-nephrosis and nephritis on the other hand had a low complementary power of their serum.

As stated before, it is not at all certain whether the mentioned qualities of the complement will always be found with the above-mentioned diseases. The clinical experience does not yet permit us to express an opinion about this and it is certainly not justified with reference to complement estimations to draw conclusions as to diagnosis. We should rather say with Osborn: »Very much more work is inquired before the clinical significance of complement estimations can be assessed . . .», the reason why I confine myself in what follows to the communication of some observations made on two patients.

*Observations taken with the investigation of serum of patient N.*

In order to investigate the connection between the complement function of serum and the clotting-temperature, at which this serum had been expressed, three blood-samples of patient N. were kept directly after venepuncture, respectively at 0° C, at room-temperature and at 37° C. To our astonishment the serum expressed at 0° C, an at 17° C did not contain complement at all. On the other hand the complementary power of serum expressed at 37° C was quite normal. The figure found was 43.

A few days afterwards the experiment was repeated wit the same results. Soon it appeared that this remarkable behaviour of the serum of patient N. had no connection with the coagulation process. For expressed at 37° C and so complement-containing serum of our patient, lost at 0° C already in a very short time its complementary power. The reverse was not the case, that is to say, the complementary power of a not active or little active portion of serum did not increase at 37° C. We concluded from this *a sensitiveness of the complement of patient N. against the influence of a low temperature.* This phenomenon is the more remarkable as it is a general experience, which I have repeatedly been able

to confirm with normal sera, that the complement retains its activity longer at a low than at a higher temperature.

A few days later the phenomenon found was subjected to a more detailed test. Now it appeared that a change had taken place in that sense that the cooling of the serum resulted, it is true, in a considerable fall, but no longer in a total disappearance of the complementary action. Now some portions of the serum of patient N. and portions of normal serum were kept at various temperatures

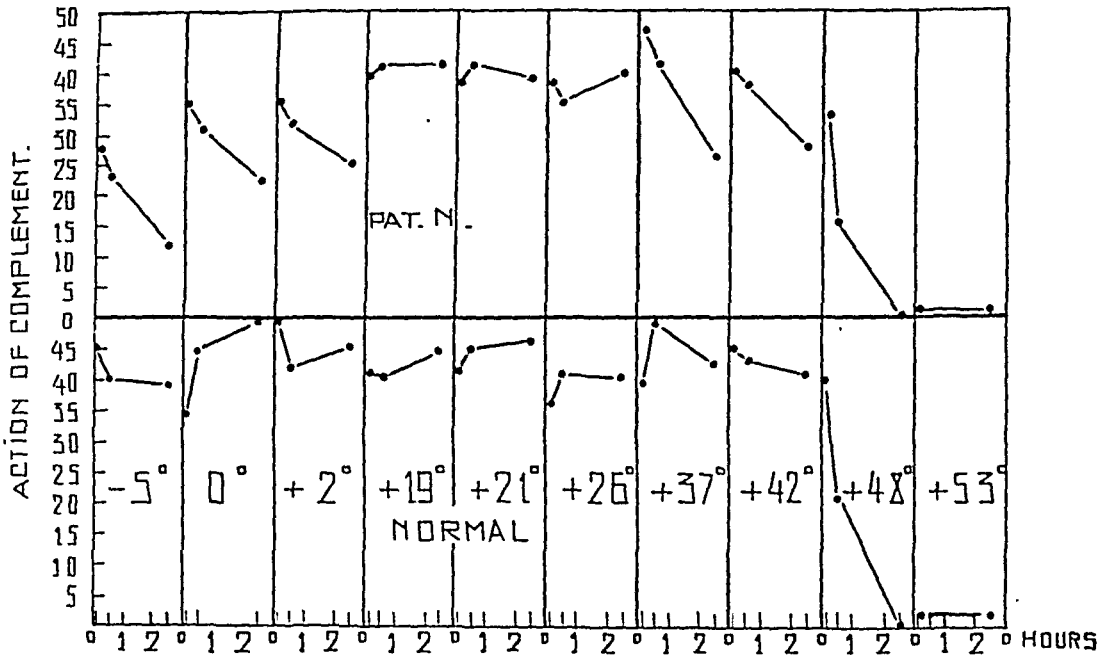



FIG. 10. RESISTANCE OF COMPLEMENT TO DIFFERENT TEMPERATURES. COMPARISION OF NORMAL SERUM WITH SERUM FROM PAT. N.

and after two and a half hours everytime the complementary power was tested. From de accompanying grafic (fig. 10) the results of this experiment may be read off.

Normal serum appears not to have decreased in complementary power after having been at temperatures of —5° C to 42° C inclusive and at 48° C to have lost after a short time half and after two and a half hours its entire complementary power.

Quite differently the serum of patient N. behaves. Only at from 19° C to 26° C inclusive this serum retains it complete power. Both at low and at higher temperatures a distinct fall is discernible. *So there exists in patient N.'s serum not only an abnormal sensitiveness*

*against low but also against high temperatures*, as regards the complementary power of this serum.

This deviating conduct both against the influence of high and low temperatures does not appear durable in the course of some weeks, as is shown in fig. 11.

Some details can be added to these observations. In the first place it has appeared that the presence of 0.38 % of sodium citrate in the serum lessens the sensitiveness against cold. *Citrate protects so to say this complement against cooling.* Only at higher temperatures

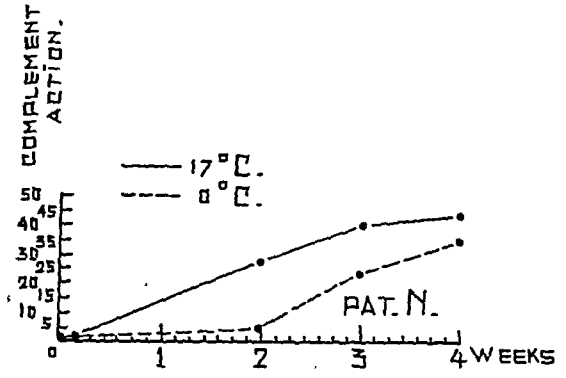



FIG. 11. ALTERATION OF TEMPERATURE INFLUENCE WITH COMPLEMENT-ACTION.

the well-known checking influence of this substance on the complement finds expression (fig. 12). In experiments with plasma the same results were obtained as with serum to which citrate had been added.

Also along another way the influence of citrate on the complementary power of this serum could be pointed out. At first the complementary power of the serum of patient N. dropped by keeping it a short time. When citrate was present no fall could be observed in 24 hours. In the course of some weeks this phenomenon is no longer to be found either.

Just as citrate protects the complement of patient N. against cooling, so $CO_2$ appears to protect it against the influence of higher temperatures. In $CO_2$ this complement appears even better proof against higher temperatures than the complement of normal serum (see fig. 13).

As said before all the mentioned particulars disappeared in course of time, so that after a good four weeks the serum of patient N. behaved almost quite normally as regards the complementary

action. So it was obvious that we investigated, whether circumstances of a temporary nature had arisen before the beginning of our observation which had given cause to the above-mentioned experiences. At the beginning of our experiments patient N. had indeed hardly recovered from a very violent angina follicularis, at which a large dose of sulfanilamide had been administered to him. So it was obvious that we investigated in how far the deviation found by us might on the one hand be dependent on the disease on the

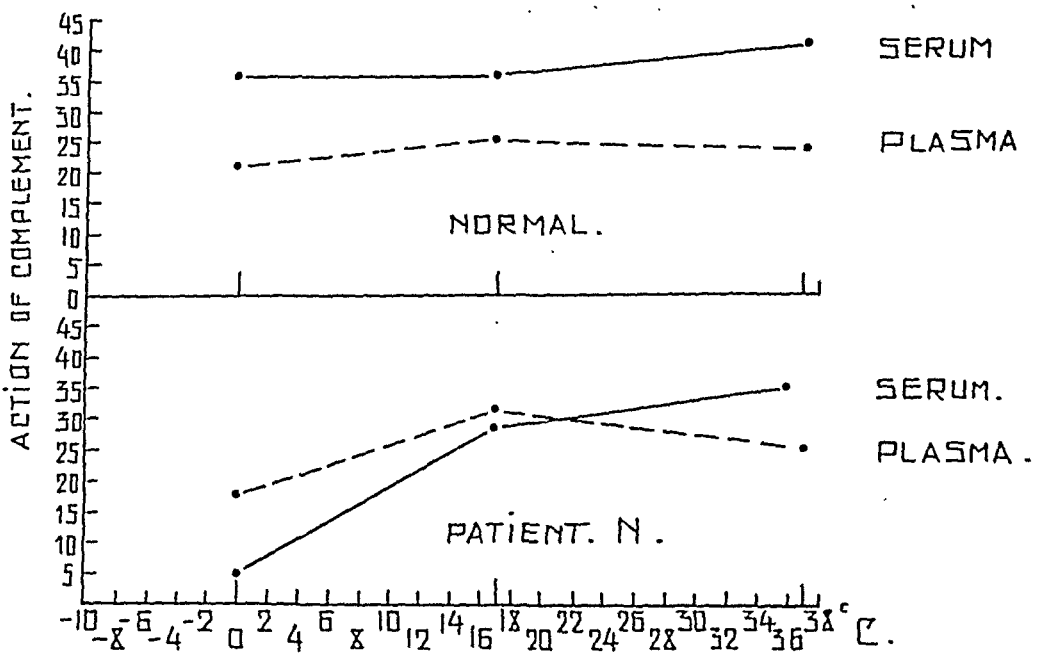



FIG. 12. COMPLEMENT INHIBITING AND PROTECTING ACTION OF CITRATE (SERUM FROM PATIENT N).

other on the therapy. Points of contact for this I have not yet been able to find or hardly to find for the present. By numerous patients who used or had used this or similar drugs the investigation as described for patient N. was repeated. Up till now always with negative results. It is true that a few times in such patients a temporary fall of the complement was found, but it never became clear whether it had to be ascribed to chemotherapeutics or to the disease itself. It may be remarked here that with various fever-diseases the complementary power of the serum is generally not reduced [Cori and Radnitz, Bender and Prausnitz (6)], a fact I have been able to confirm in numerous patients who, owing to various causes, were suffering from fever. Besides I saw in some patients a fall of the

complementary power, which had appeared after use of sulfanilamide or sulfapyridine, make way for normal values at a continuous rise of the temperature.

On account of this sulfanilamide in a high concentration was added to serum in vitro. A direct estimation of the complementary power in serum with and without the addition of this drug gave invariably the same results. After a period of 6—22 hours a distinct fall of the complementary action appeared in some sera, both normal and pathological sera, in those portions to which sulfanilamide had been added. By most of the sera there was no fall.

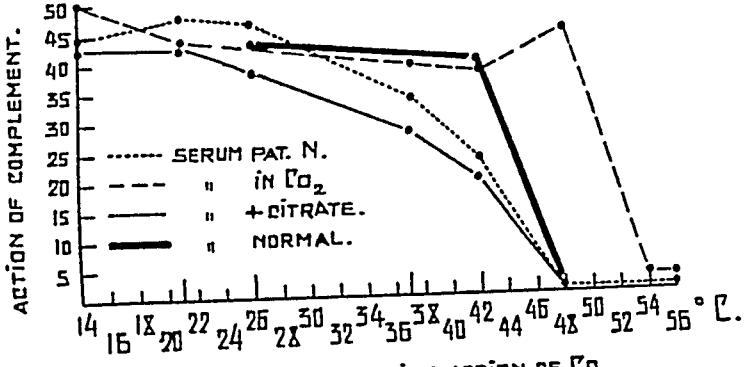



FIG. 13 COMPLEMENT PROTECTING ACTION OF $CO_2$ (SERUM FROM PATIENT N.)

*Observations taken with the investigation of serum of patient V.*

Patient V. was a woman, aged 58, who at the beginning of this investigation had already been in the clinic for a month, suffering from renal calculus with pyonephrosis. As the patient had a high temperature and kept it a long time it was supposed that the patient was suffering from urosepsis and sulfanilamide was administered. Accidentally I examined the serum of this patient on the second day of the administration of sulfanilamide and found that the serum of patient V. did not contain haemolytic complement. It did not seem justified to associate this experience with the administration of the sulfanilamide, as it had only begun the day before. It is a pity that a complement estimation before the beginning of this therapy is lacking.

Further investigation of the serum of patient V. has taught us that it was impossible to show haemolytic complement in it at whatever temperature the blood had coagulated. Nor was com-

plementary action seen in plasma or in serum to which sodium citrate had been added, neither in serum diluted with saline. Nor did it appear possible to use a heightened anti-complementary action as regards normal sera as an explanation for the phenomenon found by us. So the cause remained a mystery.

The question arose in how far this discovery of the absence of the haemolytic complement might contribute to explain the protracted fever of our patient. Did this serum perhaps miss qualities which were indispensable for, or at least of importance to bacteriolysis?

The bacteriolytical power of the serum of patient V. was tested as regards coli bacilli and was found to be quite normal. *So by patient V. the haemolytic power of the serum was lacking, whereas the bacteriolytic power, which, as is usually assumed, is a complement-function as well, was present without being disturbed.* Two possibilities were considered:

1) haemolysis requires the presence or the activity of more parts of the complement than the bacteriolysis;

2) haemolytic or bacteriolytic complement are qualities of the serum, which possess few or no common factors, so that the existence of various complements must be taken into account, at which the factors which play a part in the bacteriolysis have only as it were »accidentally» some qualities in common with the haemolytic complement.

We have not yet got to a choice of these possibilities; the investigation as regards this is still going on. But the following observations can now already be mentioned.

Starting from the supposition that only one or more parts of the complement-function should be lacking in the serum of patient V., we tried to supplement this parts, in order to compose a completely active haemolytic complement. We really succeeded in doing this to a certain extent.

That the serum of patient V. as regards the absence of haemolytic complement could not be put on a level with normal serum that had been deprived of its complementary action e. f. by heating at 56° C for half an hour, became evident through the following observation. The serum of patient V. behaved as regards the haemolysis on standing during a long time at 17° C like normal serum, whereas normal inactivated serum did not produce this phenomenon under the same circumstances. At the experiments made to try to supple-

ment the serum of patient V. use was made of a well-known method to split the complement (7). For this purpose $CO_2$ was led through normal serum 10 times diluted with water. The precipitate is dissolved in normal saline, which is equal to the quantity of serum from which we started. The fluid obtained in this way was called M, on account of the supposition that this would contain the so-called complement-midstuk.

The diluted serum is reduced after $CO_2$ has been led through, to its original volume by evaporation in a little cellophane bag. By this operation we used a hot air-current from a »Föhn»-apparatus. Care should be taken that the temperature of the liquid does not rise above 20—22° C. By means of this technique the sterility of the liquid to be prepared can be maintained. After the original serum-volume has been attained through evaporation, which can easily be verified by weighing, the preparation of liquid E is finished. It was to contain, among others, the so-called endstuk of the complement. Now both liquids, M as well as E, are examined as regards sheep's erythrocytes on isotonicity in haematocrits. Neither liquid, examined separately appears, even after the addition of amboceptor, to have haemolytic activity. Together, on the other hand, they show a distinct haemolytic complementary power, which is mostly equally strong, sometimes a little less strong, than that of the original serum out of which the two parts were prepared.

Returning to the serum of patient V., it has appeared to us that the addition of the liquid M has no effect on this serum, whereas a distinct complementary action comes to light, if *the serum of patient V. is supplemented with the liquid E.*

Serum V. inactivated before hand by heating during half an hour at 56° C is no longer capable of putting forth haemolytic complement action after the addition of E.

Apparently the serum of patient V. misses a factor which is essential to the haemolysis. This factor is to be found in the liquid E.

Besides the two factors mentioned, midstuk and endstuk (leaving undecided whether they are really separate »substances» or qualities of various serum-fractions) the presence of some other factors would be necessary for complement action, factors which as opposed to midstuk and endstuk, which would indeed be thermolabile, are thermostable. We have tried to remove some of these fractions *out of normal serum* (see Osborn p. 15 and 17). With the

products obtained we tried to supplement the serum V. again. We succeeded only with those fractions in which the endstuk had remained present. So we were allowed to suppose that, among others, the midstuk was present in the serum of patient V.

That also some thermostable factors were present in the serum of our patient, appeared when we added to this serum a small quantity of serum B. This serum B. came from a man with very low complementary power of his serum. This was due to the lack of one or more thermostable factors, which had previously been established in a similar way, as was described with the serum of patient V.

If our pre-supposition was correct then the serum B, which would miss a thermostable factor, had to be supplemented with the serum V., of which one of the thermolabile factors was missing. This was indeed the case. Serum V (complementary power: 0) + serum B (complementary power: 11) together gave a complement action of 38.

The same result, but to a somewhat smaller extent, was found, if the serum of patient V. before the experiment was heated at 56° C for 10 minutes. *Summing up we may say that the serum of patient V misses the thermolabile factor endstuk and that this factor cannot be dispensed with to bring about haemolysis.*

Starting from this supposition the bacteriolysis when haemolysis does not take place might be explained, if it would become an established fact that the factor which is lacking from the serum V. does not play a part to the bacteriolysis. Indeed we have succeeded in making this acceptable. For it has appeared to us that *the liquid M*, prepared from normal serum could already in itself, *so without the addition of the liquid E, produce strong bacteriolysis.* By heating at 56° C for half an hour this bacteriolysis failed to come about. The bacteriolysis obtained by mixing the liquids E and M is about as strong as the bacteriolysis of the original serum and of that of the liquid M alone.

For the bacteriolysis apparently fewer factors of the complement are necessary than for the haemolysis, which can explain the findings in patient V. The bacteriolytic factors are present in the fraction which was precipitated by means of $CO_2$. This fraction contains about 1/14 part of the serum proteins. The possibility exists that in this liquid M there are some haemolytic factors beside and even independent of the bacteriolytical ones. The follow-

ing experiment might plead for this opinion. We place serum of patient V. for half an hour at 37° C when sheep's erythrocytes and amboceptor are present. The erythrocytes were now centrifuged and the supernatant fluid examined both as regards haemolytic and bacteriolytic power. With the serum V. thus worked on even after the addition of the liquid E, no haemolysis could be obtained. (Serum V. which had undergone the same treatment without erythrocytes having previously been added, gave after the addition of the liquid E beautiful haemolysis). The bacteriolytic power of the serum treated in this way was on the other hand unchanged. Also experiments concerning it made with animal sera seem to lead to the conclusion that the factors essential to bacteriolysis are precipitated together with haemolytic factors by $CO_2$, but are not identical with them.

## Summary.

The results of some complement estimations in the clinic are communicated. Then a discussion follows of some remarkable findings, concerning the complement of the serum of two patients.

In one patient the complement was found to show a temporary sensitiveness not only as regards the influence of higher temperatures but also as regards cooling. Citrate protects this complement against the influence of cooling, $CO_2$ against that of higher temperatures.

In another patient it was established that the haemolytic power of the serum is lacking, but not, on the other hand, the bacteriolytic. Further investigation shows that for haemolysis more parts of the complement are necessary than for bacteriolysis. Whereas for bacteriolysis of coli bacilli the presence of midstuk alone is already sufficient, it appears that for haemolytic complement-action the presence both of midstuk and endstuk is necessary.

In various ways it is made acceptable that the serum of the patient lacks the endstuk. This explains the lack of haemolytic complement-action, when bacteriolytical power is present. It is pointed out that, although the bacteriolytical factors in preparing the midstuk precipitate together with the haemolytic, these factors need not be identical.

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Our thanks are due to Dr. J. van der Hoeden for performing the bacteriolytical tests.

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# Investigations into the Cause of the Physiological Hypoprothrombinemia in New-born Children.

## I. Investigations into the Bile Acid Production in New-born Infants.[1]

By

H. VENNDT and P. PLUM.

(Submitted for publication April 14th, 1942).

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The hypoprothrombinemic hemorrhagic diathesis in cases of biliary disease has been found to be caused by a faulty absorption of vitamin K due to a lack of bile in the intestine. (1, 3, 19). The cause of the vitamin K deficiency and the resulting hypoprothombinemia in new-born children (18, 11, 4, 7) is not clear. The following theories have been proposed: 1) deficient supply of vitamin K from the intestine (food, intestinal flora); 2) deficient supply from the mother during the latter period of the pregnancy; 3) physiological dysfunction of the liver; 4) deficient absorption of vitamin K due to a decreased production of bile acids.

In order to elucidate the last mentioned possibility, an examination has been made of the bile acid content of the gallbladder bile from a number of new-born children and, for the sake of comparison, from some infants and adults. Duodenal aspiration has not been applied, partly on account of the difficulties involved in this

[1] This work has been supported by a grant from the Rockefeller Foundation.

procedure in the case of new-born children, partly because the aspirated bile would be diluted to a highly varying degree through admixture of duodenal and pancreatic secretion. The gall-bladder bile has been collected at autopsy (12—48 hours after death), *i. e* by puncture of the gall-bladder and aspiration into a clean syringe.

## Method.

In the bile of the gall-bladder the bile acids appear in various combinations 1) in the form of cholic acid (16), partly combined with glycine and taurine: glyco- and taurocholic acid; 2) in the form of desoxycholic acid (9) and antropodesoxycholic acid (20), presumably also in connection with glycine and taurine, and finally 3) in the form of lithocholic acid, and maybe some other monoxycholanic acids in small amounts.

Formerly, most investigators presumed that cholic acid and desoxycholic acid always were bound to glycine or taurine and several authors (13, 2, 5) have used this presumption as a basis for a quantitative determination of bile acids, measuring the amount of $NH_2$ isolated from glycine and the amount of S isolated from taurine. One single publication (15), however, reports the isolation of large amounts of pure cholic acid and desoxycholic acid from the bile of a patient suffering from biliary fistula with liver injuries, for which reason the procedure described cannot be employed, at any rate not in cases of pathological biles.

The present analysis does not allow a quantitative separation of antropodesoxycholic acid and desoxycholic acid, for which reason these two acids will be discussed together. According to their constitution formula, they are denoted as dioxycholanic acid, cholic acid as trioxycholanic acid, being the only compound corresponding to this constitution, and finally, lithocholic acid is referred to as monoxycholanic acid. Cholanic acid which in a chemical respect is the basis of the acids mentioned has not been demonstrated in the bile.

In the present investigations, a gravimetric method has been used which as a matter of principle must be preferred to other quantitative methods, *viz.* the gasometric, the colorimetric, the stalagmometric, and the polarimetric determinations; the three last

mentioned methods should at any rate only be applied after the best possible isolation of the bile acids from attendant substances.

As it was the aim of this work to elucidate the question as to whether the bile of the new-born might be quantitatively or qualitatively insufficient with respect to bile acids, we have investigated, partly the total amount of bile acids and partly the distribution of the individual types of acids.

The analysis (developed by H. Venndt) is based upon a principle described by Wieland and Seibert (21) for the separation of tri-, di-, and monoxycholanic acids. According to this method, the trioxycholanic acids can be extracted from an ether solution by means of 15 per cent ether-saturated hydrochloric acid. The dioxycholanic acids can be extracted with 25 per cent ethersaturated hydrochloric acid, while monoxycholanic acids may be found in the residual ether. The details of the method applied may be outlined in brief.

1 ml bile is pipetted into a small Erlenmeyer flask containing 15 ml of a 12 per cent KOH. Thereupon the material is autoclaved for 5 hours at 120° C.

After cooling down and adding HCl until acid reaction to Congo red, the material is shaken 3 times with ether in order to remove all ether soluble substances. After evaporation of the ether and dissolution in absolute alcohol, the dye-stuffs and some of the fatty acids are precipitated with $BaCl_2$ saturated $Ba(OH)_2$.

Immediately after addition of baryte, the sample is heated during rotation for 10 min. in a water bath of 40° C, whereupon it is left to precipitate at room temperature for 18—20 hours. The precipitate is centrifuged off, and the alcohol evaporated, whereupon the residue is taken up with a 5 per cent $Na_2CO_3$ solution. The precipitate consisting of $BaCO_3$ and compounds insoluble in $Na_2CO_3$ is centrifuged down.

Subsequently, a continuous ether extraction is performed for 6 hours at alcaline reaction in a special apparatus constructed by Müller. (10)

After the $Na_2CO_3$ solution has become acid to Congo red, the extraction with ether is repeated, and from the ether, the final differentiated extraction of the bile acids by means of 15 and 25 per cent ether-saturated HCl is performed, as previously described. Finally, the isolated amounts are transferred into small scales by means of alcohol. Heating at 110° C for 1 hour after evaporation of the alcohol removes the alcohol bound to the bile acids, which then may be determined by weighing after cooling.

The method gives reliable results for the total amount of bile acids (the sum of the 3 fractions).

The determination of the individual fractions is, however, subject to a greater error which will be least when the quantities of acid extracted with 15 and 25 per cent ether-saturated HCl are almost equally large, as has been the case in most of the bile samples investigated in connexion with this work.

In cases where pure cholic acid or pure desoxycholic acid occur, up to 10 per cent can be determined as belonging to the other fraction; in a less unfavourable distribution of the acids the divergencies will become correspondingly smaller.

The acids remaining in the residual ether which according to Wieland and Seibert mainly consist of monoxycholanic acids, were, however, as a rule found to be dominated by dioxycholanic acid, which acid was not removed completely by extraction with 25 per cent ether-saturated HCl, except when present in very small amounts. Hence, the determination of this fraction permits only a rough estimation.

The above-mentioned error in the determination of the acid extracted with 15 and 25 per cent ether-saturated HCl, respectively, will be the same in different samples, when the proportion between the tri- and dioxycholanic acids is the same. A more exact estimation of the results can be made by a comparison with the analytic results from model experiments started with known amounts of acids. This method has not, however, been applied to the results reported.

## Material.

The investigations have been carried out on a material comprising as far as possible all autopsies performed within a given period at the Blegdamshospital (only children), the Rigshospital, and the Institute of Forensic Medicine, University of Copenhagen (from cadavers where death was caused by trauma). — The material comprises (1) 15 new-born children, (2) 11 infants of 1—12 months of age, (3) 2 children, 4 and 7 years old, and (4) 22 adults; a total of 50.

## Results.

*1. New-born children.* The material comprises 1 child (case report Nr. 159 G/40) who died of hypoprothrombinemic hemorrha-

gic diathesis, 3 children born at full term but still-born, and, finally, 11 children who were born between 1 and 12 weeks before term.

**Table 1.**

Bile acid content of the gall-bladder bile of new-born children.[1]

| Case report Nr.[2] | Sex | Weight | State at birth | Time of birth | Lifetime in hours | Bile acids in mg per ml. | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Total amount | Dioxy-cholanic acid | Trioxy-cholanic acid |
| 629 A/40 | F | 4650 | asphyctic | at full term | 0 | 4.9 | 2.2 | 2.7 |
| 453 A/40 | M | 3500 | macerated | at full term | 0 | 8.8 | 4.4 | 4.4 |
| 460 A/40 | M | 3350 | still-born | at full term | 0 | 10.7 | 5.0 | 5.2 |
| 671 A/40 | M | 3200 | asphyctic | 1—2 weeks b. t. | 29 | 3.0 | 1.5 | 1.5 |
| 703 A/40 | M | 2500 | still-born | 2—3 weeks b. t. | 0 | 6.6 | 2.9 | 3.7 |
| 599 A/40 | F | 2400 | still-born | 3—4 weeks b. t. | 0 | 4.8 | 1.9 | 2.9 |
| 159 G/40 | M | 2400 | alive | 4 weeks b. t. | 72 | 6.1 | 4.0 | 2.1 |
| 525 A/40 | M | 2300 | still-born | 4—5 weeks b. t. | 0 | 7.3 | 2.8 | 3.7 |
| 457 A/40 | M | 1900 | asphyctic | 5—6 weeks b. t. | 5 | 4.5 | 3.0 | 1.5 |
| 653 A/40 | M | 1550 | still-born | 6—7 weeks b. t. | 0 | 10.0 | 5.0 | 5.0 |
| 655 A/40 | F | 1450 | alive | 8 weeks b. t. | 12 | 5.2 | 2.9 | 2.3 |
| 592 B/40 | F | 1350 | severely mac. | 8 weeks b. t. | 0 | 5.4 | 3.1 | 2.3 |
| 586 B/40 | F | 1150 | slightly mac. | 10—12 weeks b. t. | 0 | 2.2 | 1.8 | 0.4 |
| 679 A/40 | M | 1200 | alive | 10—12 weeks b. t. | 48 | 7.7 | 4.1 | 3.6 |
| 739 B/40 | M | 1000 | still-born | 10—12 weeks b. t. | 0 | 2.0 | 1.0 | 1.0 |

It appears from table 1 that bile acids are present even in the gall-bladder bile of children born 2—3 months before term and that no relation exists between the percental bile acid content found and the time of birth.

*2. Infants.* The material consists of 11 children between 1 and 12 months of age, 9 of which died of infectious diseases, 1 of chronic dyspepsia with attendant adipose degeneration of the liver, 1 of congenital pyloric stenosis, and 1 of hypoprothrombinemic hemorrhagic diathesis.

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[1] Our thanks are due to Professor Poul Moller, M. D., Professor Knud Sand, M. D., and Professor H. C. A. Lassen, M. D., for the permission to use the material and case reports.

[2] A = Rigshospital, Department of Obstetrics, A.
B = Rigshospital, Department of Obstetrics, B.
G = Rigshospital, Department of Pediatrics.

**Table 2.**

Bile acid content of the gall-bladder bile of children 1—12 months of age.

| Hospital | Case report Nr. | Sex | Age in months | Diagnosis | Bile acids in mg per ml. | | |
|---|---|---|---|---|---|---|---|
| | | | | | Total amount | Dioxycholanic acid | Trioxycholanic acid |
| R. H. Dept. G | 146/40 | F | 1 ½ | Pneumonia | 25.7 | 7.3 | 16.8 |
| R. H. Dept. G | 458/40 | M | 3 | Congenital pyloric stenosis | 12.4 | 7.2 | 5.2 |
| R. H. Dept. G | 228/40 | M | 3 | Gastro-enteritis. Hypoprothrombinemic hemorrhagic diathesis | 1.8 | 0.7 | 1.1 |
| Bl. H. | 5414/40 | M | 4 ½ | Bronchopneumonia | 4.5 | 2.0 | 2.5 |
| Bl. H. | 5444/40 | M | 4 ½ | Pyelonephritis. Hypoprothrombinemic hemorrhagic diathesis | 13.5 | 8.8 | 4.5 |
| R. H. Dept. G | 219/40 | M | 6 | Meningococcus meningitis | 7.3 | 5.0 | 2.3 |
| R. H. Dept. G | 525/40 | F | 6 | Chronic intestinal indigestion. Fatty degeneration of the liver. Hypoprothrombinemic hemorrhagic diathesis | 8.6 | 5.6 | 3.0 |
| Bl. H. | 4881/40 | F | 8 | Pyogenic meningitis | 3.0 | 1.6 | 1.4 |
| Bl. H. | 4594/40 | M | 8 | Pyogenic meningitis | 17.7 | 8.9 | 9.8 |
| Bl. H. | 5236/40 | F | 11 | Pertussis. Bronchopneumonia | 19.3 | 10.3 | 9.0 |
| Bl. H. | 5015/40 | M | 12 | Pertussis. Capillary bronchitis | 6.3 | 3.5 | 2.8 |

R. H. = Rigshospital. Bl. H. = Blegdamshospital.

Table 2 reveals that the values found in the first year of life are — on an average — somewhat higher than the values found in the new-born and that this group of children also shows a considerable variation of the values, without any relation to age.

*3. Older Children.*

**Table 3.**

The bile acid content of the gall-bladder bile of 2 older children.

| Hospital | Case report Nr. | Sex | Age in years | Diagnosis | Bile acids in mg per ml. | | |
|---|---|---|---|---|---|---|---|
| | | | | | Total amount | Dioxycholanic acid | Trioxycholanic acid |
| Bl. H. | 3444/40 | F | 4 | Bronchopneumonia. Myocarditis. | 15.9 | 8.5 | 7.4 |
| I. F. M. | Sdr. B. Nov.8th 1940 | M | 7 | Fractures of the skull. Intracranial hemorrhage. | 54.6 | 23.2 | 26.4 |

Bl. H. = Blegdamshospital. I. F. M. = Institute of Forensic Medicine.

*4. Adults.* The material is arranged in three groups, *viz.* 1) 5 persons who died after an accident, dissected at the Institute of Forensic Medicine, 2) 11 adults who died at the Rigshospital of medical or surgical diseases without signs of liver disease, and 3) 6 adults who died at the Rigshospital of medical or surgical diseases with signs of liver injuries.

## Discussion.

It is seen from the tables that the bile acid content of the gall-bladder bile of new-born children has been found lying between 2.0 and 10.6 mg per ml. Infants showed an even distribution between 1.8 and 25.7 mg per ml, two thirds of the cases, however, lying below 15 mg per ml. Adults without liver disease gave values between 13.4 and 72.8 mg per ml, 9 out of 16 lying between 30 and 60 mg per ml. The values found in adults suffering from liver disease were between 2.2 and 22.7 mg per ml, 4 out of 6 being below 10 mg per ml (see also figure).

The investigations show that the gall-bladder bile of new-born children, full term as well as prematurely born, contains bile acids of almost the same qualitative composition as in older children and adults. The amount of bile acids per ml is, however, smaller in the

**Table 4.**

The bile acid content of the gall-bladder bile of adults.

| Hospital | Case report Nr. | Sex | Age in years | Diagnosis | Bile acids in mg per ml. | | |
|---|---|---|---|---|---|---|---|
| | | | | | Total amount | Dioxy-cholanic acid | Trioxycho-lanic acid |
| I. F. M. | D. 183 | M | 38 | Fractures of the skull. Brain contusion and cerebral hemorrhage | 58.2 | 27.7 | 21.4 |
| I. F. M. | E. 33 | F | 53 | Fracture of the skull. Brain contusion and cerebral hemorrhage | 72.8 | 41.2 | 23.5 |
| I. F. M. | D. 176 | M | 61 | Fracture of the skull. Brain contusion and cerebral hemorrhage | 33.2 | 16.0 | 14.5 |
| I. F. M. | D. 170 | F | 66 | Embolus of the pulmonary artery. Thrombosis of the femoral artery. Fracture of the left malleolus | 34.2 | 21.8 | 8.3 |
| I. F. M. | D. 171 | M | 83 | Fracture of the cervical spine. Contusion of the cervical spinal cord | 36.1 | 25.7 | 7.7 |
| Dept. C | 138/40 | M | 22 | Graves' disease. Sequelæ strumectomia. Bronchopneumonia. | 40.7 | 23.0 | 17.7 |
| Dept. A | 152/40 | M | 30 | Migratory Pneumonia. Left pulmonary abscess. | 13.4 | 6.3 | 7.1 |
| Dept. N | 140/40 | M | 35 | Subarachnoidal hemorrhage. Sequelæ craniotomia. Bronchopneumonia | 45.7 | 28.6 | 17.1 |
| Dept. D | 129/40 | F | 42 | Ulcerative colitis. Diffuse peritonitis. | 24.6 | 2.0 | 22.6 |
| Dept. C | 114/40 | M | 44 | Nephrolithiasis. Sequelæ nephrectomia. | 42.4 | 22.6 | 19.6 |
| Dept. N | 130/40 | M | 45 | Cerebral tumor. Sequelæ craniotomia. Pneumonia. | 46.3 | 43.3 | 3.0 |

Table 4 (continued).

| Hospital | Case report Nr. | Sex | Age in years | Diagnosis | Bile acids in mg per ml. | | |
|---|---|---|---|---|---|---|---|
| | | | | | Total amount | Dioxy-cholanic acid | Trioxycho-lanic acid |
| Dept A | 139/40 | M | 54 | Left pulmonary cancer | 73.6 | 40.2 | 33.4 |
| Dept. O | 148/40 | M | 59 | Senile dementia. Bronchopneumonia. | 22.3 | 15.9 | 6.4 |
| Dept. B | 124/40 | M | 62 | Coronary thrombosis. | 43.1 | 25.0 | 18.1 |
| Dept. F | 150/40 | F | 67 | Right maxillary sarcoma. Bronchopneumonia. | 27.8 | 20.1 | 7.7 |
| Dept. B | 113/40 | M | 73 | Cerebral hemorrhage. Bronchopneumonia. Cholelithiasis. | 22.4 | 13.0 | 9.4 |
| Dept. of Obst. | 136/40 | F | 39 | Right pulmonary infarct. Fatty degeneration of the liver. | 2.8 | 1.4 | 1.4 |
| Dept. B | 146/40 | M | 46 | Gastro-colic fistula. Icterus. Avitaminosis. | 8.9 | 6.0 | 2.9 |
| Dept. D | 135/40 | M | 65 | Cancer of the stomach. Metastases to the liver. | 2.2 | 0.9 | 1.3 |
| Dept. B | 128/40 | F | 66 | Lymphatic leukemia. Lymphatic infiltration of the liver. | 22.7 | 11.9 | 10.8 |
| Dept. C | 142/40 | M | 69 | Hypertrophy of the pros tate. Uremia. Bronchopneumonia. Parenchymatous degeneration of the liver. | 12.4 | 7.7 | 4.7 |
| Dept. B | 131/40 | M | 84 | Cancer of the stomach. Cholelithiasis. | 4.7 | 2.7 | 2.0 |

I. F. M. = Institute of Forensic Medicine. The rest are departments of the Rigshospital.

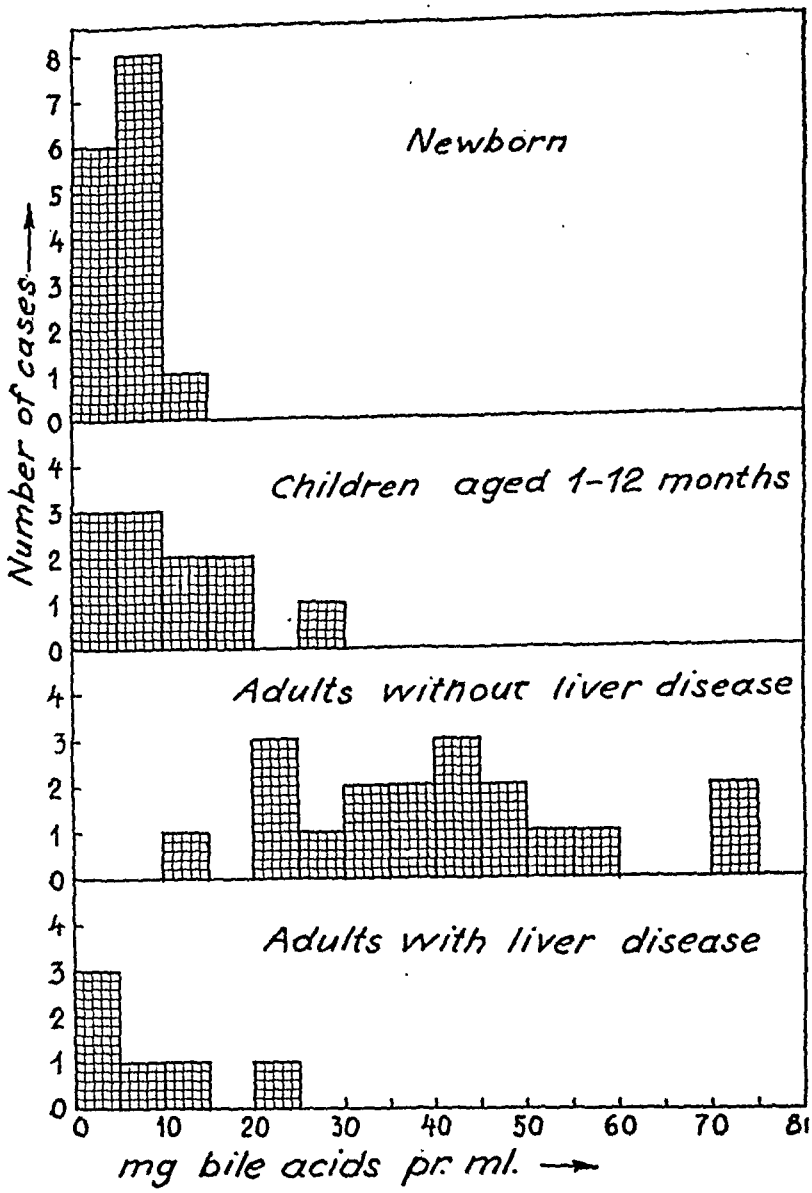



Fig. 1. Distribution of the values of bile acids in gall-bladder bile in the four groups investigated.

case of new-born children than in adults without liver disease, while it does not differ very much from the values obtained in infants between 1 and 12 months of age. The latter group, however, often shows higher values than any of the newborn children. In adults suffering from liver disease, the amount of bile acids was found to be low, *viz.* of the same order of magnitude as in infants.

The low values found in new-born children do not suffice to clear up the question of a possibly deficient absorption of the fat

soluble vitamin K, the secreted amount of bile and the amount of bile acids necessary for absorption being unknown.

## Conclusion.

The low content of bile acids in the gall-bladder bile of new-born, children can scarcely explain the K-avitaminous hypoprothrombinemia during the first days of life; it may, however, be considered an additional factor.

## Summary.

1. In new-born children, prematurely as well as full term born, the authors found a concentration of bile acids in the gallbladder bile obtained by autopsy between 2 and 10.7 mg per ml.

2. Infants between 1 and 12 months of age showed values evenly distributed between 1.8 and 25.7 mg per ml. Two children of 4 and 7 years of age had 15.9 and 54.6 mg per ml, respectively.

3. Adults without liver disease gave values between 13.4 and 73.6 mg per ml. Adults suffering from liver disease were found to have between 2.2 and 22.7 mg per ml.

4. In all groups, the distribution of the bile acid fractions investigated was found to be the same.

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(From the Portuguese Jewish Hospital at Amsterdam).

# The influence of synthetical vitamin K upon the agglutinating power of serum.

By

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In a correspondence in »the Journal of the American Medical Association» of March 22. 1941 J. K. Narat mentioned that serum of patients, who had received an intramuscular injection of vitamin K, agglutinated red cells of the A-, B- and O-group; 3 mg synthetical vitamin K (which preparation was not mentioned) was administered by intramuscular injection. The changed agglutination lasted for about two weeks. This observation of Narat stimulated us to repeat this experiment and, if we could confirm Narats findings, to inquire into the following questions:

1. how much time after the application of synthetical vitamin K, can the agglutination be established of red cells of the blood-group, which are not agglutinated before, and what is the smallest quantity of vitamin K required to induce the change?

2. how long does this phenomenon last?

3. is there any difference between the influence of application of the vitamin K orally and by intramuscular injection?

4. does the vitamin K influence the agglutination of the red cells of those groups, which were agglutinated before the application of the vitamin K?

5. does the addition of vitamin K to serum in vitro alter the agglutination?

6. is the influence on the agglutination of the different synthetical preparations of the vitamin K the same?

I. First of all the agglutination of A-, B- and O-red cells by serum of patients was studied before, and 24 hours after *oral administration* of the vitamin K preparation: beta. methyl. naphthohydrochinon-disulfaatnatrium (davitamon K made by Organon Holland).

After the oral application of 10, 20 and 30 mg davitamon K no change of the agglutination was noticed. After 40 mg distinct change of the agglutination was observed.

In the subjoined schedule the results of the examination of ten cases [1] belonging to different bloodgroups are to be seen.

**Table I.**

| Bloodgroup of patient | | Before administration of davitamon K | | | After administration of 40 mgr. da vitamon K orally | | |
|---|---|---|---|---|---|---|---|
| | | + Serum of patient + red cells A | + Serum of patient + red cells B | + Serum of patient + red cells O | + Serum of patient + red cells A | + Serum of patient + red cells B | + Serum of patient + red cells O |
| I | B | + | — | — | + | — | + |
| II | B | + | — | — | + | + | + |
| III | A | — | + | — | + | + | + |
| IV | O | + | + | — | + | + | + |
| V | O | + | + | — | + | + | + |
| VI | A | — | + | — | + | + | + |
| VII | A | — | + | — | — | + | + |
| VIII | A | — | + | — | — | + | + |
| IX | O | + | + | — | + | + | + |
| X | A | — | + | — | — | + | + |

We also examined the agglutination of the red cells of the patients I—X by serum of the bloodgroups A, B and O; as no influence was noticed, the results are not recorded in the schema. From table I we may conclude that after the oral application of 40 mg beta. methyl. naphthohydrochinon-disulfaatnatrium, the serum of the patient agglutinates in all cases the red cells of the O-group and in the majority of the cases also the red cells of the group, which the blood of the patient belongs to. Maximal effect was noticed 24 hours after oral administration. The agglutination was normal again 48 hours after the oral application.

[1] The patients, in whom the vitamin K effect upon the agglutination was studied in this investigation, were all reconvalescent adult patients, not suffering from a disease of the intestinal tract or from an hepatic disorder.

Auto agglutination was never observed.

II. The smallest quantity of vitamin K. which had to be given intramuscularly to bring about a change in the agglutination, when we made use of davitamon K, proved to be 30 mg. The first alteration appeared already one hour and a half after the intramuscular injection. The effect was most apparent 24 hours after the application and vanished 3 days after the intramuscular injection. So the effect started earlier than after oral administration and lasted longer.

In order to learn more about this agglutination, the agglutination-titer of the serum before and after oral and intramuscular administration of davitamon K was determined. For this purpose the patients' serum was diluted with physiological saline solution according to the following dilutions: 1: 2 ½, 1: 5, 1: 10, 1: 25, 1: 50, 1: 100 and 1: 200. As agglutinationtiter was indicated the last dilution, which still agglutinated the erythrocytes.

The following first five schedules refer to the agglutination by serum of patients, who had received an intramuscular injection of 30 mg davitamon K, the other five to the agglutination of serum of patients, who had taken 40 mg davitamon K orally.

| | Red cells A aggl. titer | Red cells B aggl. titer | Red cells O aggl. titer |
|---|---|---|---|
| I ♀ 33 yr. bloodgroup A | | | |
| serum of patient before the injection | — | + 1: 25 | — |
| " " " 1 ½ hrs. after " | — | + 1: 25 | + 1: 25 |
| " " " 24 " " " | — | + 1: 25 | + 1: 100 |
| " " " 48 " " " | — | + 1: 25 | + 1: 25 |
| " " " 72 " " " | — | + 1: 25 | — |
| II ♂ 18 yr. bloodgroup B | | | |
| serum of patient before the injection | + 1: 5 | — | — |
| " " " 1 ½ hrs. after " | + 1: 5 | + 1: 2 ½ | — |
| " " " 24 " " " | + 1: 5 | + 1: 10 | + 1: 2 ½ |
| " " " 48 " " " | + 1: 5 | + 1: 5 | + 1: 0 |
| " " " 72 " " " | + 1: 5 | — | — |
| III ♀ 52 yr. bloodgroup O | | | |
| Serum of patient before the injection | + 1: 10 | + 1: 10 | — |
| " " " 1 ½ hrs. after " | + 1: 10 | + 1: 10 | + 1: 10 |
| " " " 24 " " " | + 1: 10 | + 1: 10 | + 1: 25 |
| " " " 48 " " " | + 1: 10 | + 1: 10 | + 1: 0 |
| " " " 72 " " " | + 1: 10 | + 1: 10 | — |

| | Red cells A agglt. titer | Red cells B agglt. titer | Red cells O agglt. titer |
|---|---|---|---|
| IV ♀ 56 yr. bloodgroup A | | | |
| serum of patient before the injection | — | + 1:10 | — |
| » » » 1½ hrs. after » | + 1:0 | + 1:10 | + 1:5 |
| » » » 24 » » » | + 1:2½ | + 1:10 | + 1:10 |
| » » » 48 » » » | — | + 1:10 | + 1:0 |
| » » » 72 » » » | — | + 1:10 | — |
| V ♀ 47 yr. bloodgroup B | | | |
| serum of patient before the injection | + 1:25 | — | — |
| » » » 1½ hrs. after » | + 1:25 | + 1:5 | + 1:10 |
| » » » 24 » » » | + 1:25 | + 1:10 | + 1:25 |
| » » » 48 » » » | + 1:25 | + 1:0 | + 1:2½ |
| » » » 72 » » » | + 1:25 | — | — |
| VI ♂ 54 yr. bloodgroup O | | | |
| Serum of patient before oral admin. | + 1:10 | + 1:10 | — |
| » » » 24 hrs. after » » | + 1:10 | + 1:10 | + 1:0 |
| » » » 48 » » » » | + 1:10 | + 1:10 | — |
| VII ♀ 75 yr. bloodgroup O | | | |
| serum of patient before oral admin. | + 1:25 | + 1:25 | — |
| » » » 24 hrs. after » » | + 1:25 | + 1:25 | + 1:2½ |
| » » » 28 » » » » | + 1:25 | + 1:25 | — |
| VIII ♂ 56 yr. bloodgroup O | | | |
| serum of patient before oral admin. of vitamin K | + 1:25 | + 1:50 | — |
| serum of patient 24 hrs. after oral admin. of vitamin K | + 1:25 | + 1:50 | + 1:2½ |
| serum of patient 48 hrs. after oral admin. of vitamin K | + 1:25 | + 1:50 | — |
| IX ♀ 32 yr. bloodgroup A | | | |
| serum of patient before oral admin. of vitamin K | — | + 1:25 | — |
| serum of patient 24 hrs. after oral admin. of vitamin K | + 1:2½ | + 1:25 | + 1:2½ |
| serum of patient 48 hrs. after oral admin. of vitamin K | — | + 1:25 | — |
| X ♀ 61 yr. bloodgroup O | | | |
| serum of patient before oral admin. of vitamin K | + 1:10 | + 1:5 | — |
| serum of patient 24 hrs. after oral admin. of vitamin K | + 1:10 | + 1:5 | + 1:0 |
| serum of patient 48 hrs. after oral admin. of vitamin K | + 1:10 | + 1:5 | — |

From these schedules was concluded that the titer of the agglutination, which occurred after oral and intramuscular administration of davitamon K was highest 24 hours after the application and run in the different cases about parallel to the rate of the titer of the agglutination, which existed before the administration of davitamon K.

The titer of the agglutination existing before the davitamon K was taken, was not influenced by the vitamin K.

The agglutination which appeared after oral application of 40 mg davitamon K, was very slight, the highest titer being 1: 2 ½.

We also added davitamon K to serum in vitro (5 dr. to 1 $cm^3$) and incubated this serum during three hours at 37°. However no change in the agglutination was remarked in this way.

We also studied the effect on the agglutination of two other synthetical vitamin K preparations;

A. synkavit (Hoffmann-La Roche): 2 methyl-1.4 bisuccinyl-naphthohydrochinon.

After intramuscular injection of already 3 mg in a case belonging to the O-group, slight agglutination of the O-red cells was observed (the titer being only 1: 0) and this effect had disappeared after 72 hours.

6 mg Synkavit injected in the muscles, caused in another case, belonging to the O-group, an agglutination of the O-red cells of an high titer (1: 50); this agglutination was most apparent 24 hours after the injection and had vanished 5 days after the application.

B. Solvika (Amsterdamsche Chininefabriek): 4-amino-2 methyl-1 naphtholhydrochloride. 3 mg administered by intramuscular injection caused an extra-agglutination, the highest titer being 1: 2 ½; the effect was gone 72 hours after the injection. The effect of 6 mg applicated by intramuscular injection lasted the same time, the titer being higher (1: 25 in one case).

*Comment.*

In this investigation we thus have confirmed and extended Narats findings.

After administration of synthetical vitamin K, serum of the A-group agglutinated red cells of the O-group or both the A- and O-red cells; serum of the B-group agglutinated the O-red cells or the B- and O-red cells. Serum of the O-group agglutinated the red cells of the O-group.

In none of the cases auto-agglutination did appear.

The effect lasted after intramuscular injection of 30 mg beta-methyl-naphthohydrochinon disulfaatnatrium two days, after oral application of 40 mg one day.

Oral application of less than 40 mg davitamon K had no effect. 30 mg davitamon K was the smallest quantity, which had to be injected intramuscularly, to cause a change of the agglutination. The titer of the agglutination, which existed before the administration of the vitamin K, was not influenced.

The titer of the abnormal agglutination, after intramuscular injection of 30 mg davitamon K, was of the same intensity as or higher than the normal agglutination titer of the serum.

When we made use of 2 methyl- 1.4 bisuccinyl-naphthohydrochinon, the abnormal agglutination appeared after the intramuscular injection of a much smaller quantity; already 3 mg caused an abnormal agglutination of a rather low titer. 6 mg caused an extra agglutination, which had the same titer as that of the agglutination existing before the application and which lasted 4 days.

3 mg 4 amino-2 methyl- 1 naphtholhydrochloride (Solvika) applicated by intramuscular injection, gave also rise to an abnormal agglutination of a low titer.

6 mg effected an abnormal agglutination lasting two days. It is therefore most likely that the transfusion of blood to a patient to whom synthetical vitamin K has been administered till 48 hours before the transfusion, may give rise to difficulties and even may prove impossible. It must be mentioned that a dose of 6 mg 2 methyl-1.4 bisuccinyl-naphthohydrochinon (synkavit) does change the agglutination during a period of 4 days.

## Conclusion.

The effect of different synthetical vitamin K preparations, administered orally and intramuscularly, upon the agglutinating power of the serum of a number of patients was studied.

The observation of J. K. Narat was confirmed.

We have laid stress upon the harmfull consequences, which these passing alterations of the agglutinating power of the serum can afflict upon a bloodtransfusion, which has been lately preceded by the application of synthetical vitamin K.

I wish to thank Professor S. van Creveld for his critical remarks.

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(Aus dem St. Josef Krankenhaus, Deventer (Holland); Director: Dr A. W. M. Pompen.)

# Beitrag zu der Differentialdiagnose der Erythrodermischen Form der Hodgkinschen Krankheit.

Von

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(Bei der Redaktion am 7. April 1942 eingegangen).

Vor einigen Jahren wurde von Pautrier und Woringer das Vorkommen starker Lymphdrüsenschwellungen bei Erythrodermien verschiedener Art beschrieben, wobei die vergrösserten Lymphdrüsen ein sehr charakteristisches histopathologisches Bild darbieten, das von ihnen *Réticulose lipomélanique* [1] genannt wird. Die Struktur der Lymphfollikel bleibt im Allgemeinen erhalten; das Retikulum hat, besonders im kortikalen Teile, stark zugenommen (sog. Reticulum-plâques); die Lymphsinusse sind prall mit polymorphen Zellen, besonders vielen eosinophilen, gefüllt. Ferner werden in wechselnd starkem Masse mit Lipoid und Melaninpigment gefüllte Zellen angetroffen.

Das Kennen dieses Bildes ist für die Praxis nicht ohne Bedeutung; namentlich beim Diagnostizieren von Fällen von Lymphogranuloma malignum [2], die von einer Erythrodermie begleitet werden, ist es notwendig zu wissen, dass auch Erythrodermien anderen

[1] L. M. Pautrier, Fr. Woringer. Ann. de derm. et syph. *8*, 257—273, April 1937.

[2] Mutatis mutandis gilt diese Betrachtung für andere Krankheiten, die mit Erythrodermie verbunden sind, und bei denen die klinische Untersuchung über die Art des Prozesses keinen Aufschluss gibt.

Ursprunges und im allgemeinen einer weniger düsteren Prognose mit Schwellung von Lymphdrüsen verbunden sein können.

Es ist, in Anbetracht der nicht immer gut zu etikettierenden pathologisch-anatomischen Abweichungen in den Lymphdrüsen bei Fällen von Hodgkinscher Krankheit, ein nicht zu unterschätzendes Hilfsmittel beim Stellen oder Ausschliessen dieser Diagnose, wenn sich zeigt, dass die vergrösserten Lymphdrüsen das von Pautrier und Woringer beschriebene kennzeichnende Bild aufweisen.

Der folgende Fall kann hierbei als Beispiel dienen:

Patient K, 72 Jahre alt, Bäcker von Beruf, wird am 27. VI. 1939 wegen einer *heftig juckenden*, generalisierten Hauterkrankung aufgenommen, die im Januar desselben Jahres entstand. Die Beine, Kniekehlen, Achselhöhlen und Ellenbogenfalten wurden zuerst befallen. Die Hauterkrankung ist nie feucht gewesen. Jetzt zeigt sich das Bild einer chronischen Erythrodermie. Die Haut glänzt etwas, ist sehr trocken und im Allgemeinen etwas verdickt; mit örtlich einer deutlichen Zeichnung der Hautfelder. Es besteht eine feine Schilferung. Auffallend ist die braune Farbe, sepiafarbig bis kupferbraun. Namentlich an den Unterarmen und Unterschenkeln befinden sich zahlreiche Kratzstellen. Pubis- und Achselhöhlenbehaarung sind nahezu ganz verschwunden; dies ist auch teilweise mit den Augenbrauen der Fall. Die Schleimhäute zeigen keine Abweichungen. Unter dem linken Kieferwinkel befindet sich eine grössere Hervorwölbung (Bild 1); dort ist ein Paket Lymphdrüsen abtastbar, deren Grösse bis an diejenige eines Taubeneies heranreicht. In den Leisten bestehen deutliche Lymphdrüsenschwellungen, ebenfalls in der rechten Achselhöhle, während links nur einige kleinere Drüsen zu fühlen sind. Weitere Lymphome findet man rechts supraklavikular. Der rechte Kieferwinkel ist Schwellungsfrei. Die geschwollenen Lymphdrüsen sind fest, nicht schmerzhaft und weder mit der Haut noch untereinander verwachsen. Es finden sich keine Zeichen von Erweichung.

Histologisches Bild der Haut:[1]

Das bedeckende Pflasterepithel ist verdickt, aber unversehrt. Es zeigt an vielen Stellen parakeratotische Verhornung. In der Cutis unter dem Epithel findet man bis zu ziemlich grosser Tiefe ein mässig gefässreiches Gewebe, das in seinem Aufbau sehr an die noch näher zu beschreibenden blassen Felder aus der Lymphdrüse erinnert. Auch hier findet man einige Lymphocyten und eosinophile Zellen. Pigment wird fast nicht angetroffen, weder im Epithel, noch unter demselben. Das neugebildete Gewebe enthält ziemlich viele Kapillaren und unterscheidet sich in den Bindegewebsfärbungen scharf von dem Bindegewebe der Cutis.

[1] Die histologischen Beschreibungen und die Mikrophotographie verdanken wir Dr H. J. G. Wijers. St. Joannes de Deo. Haag.

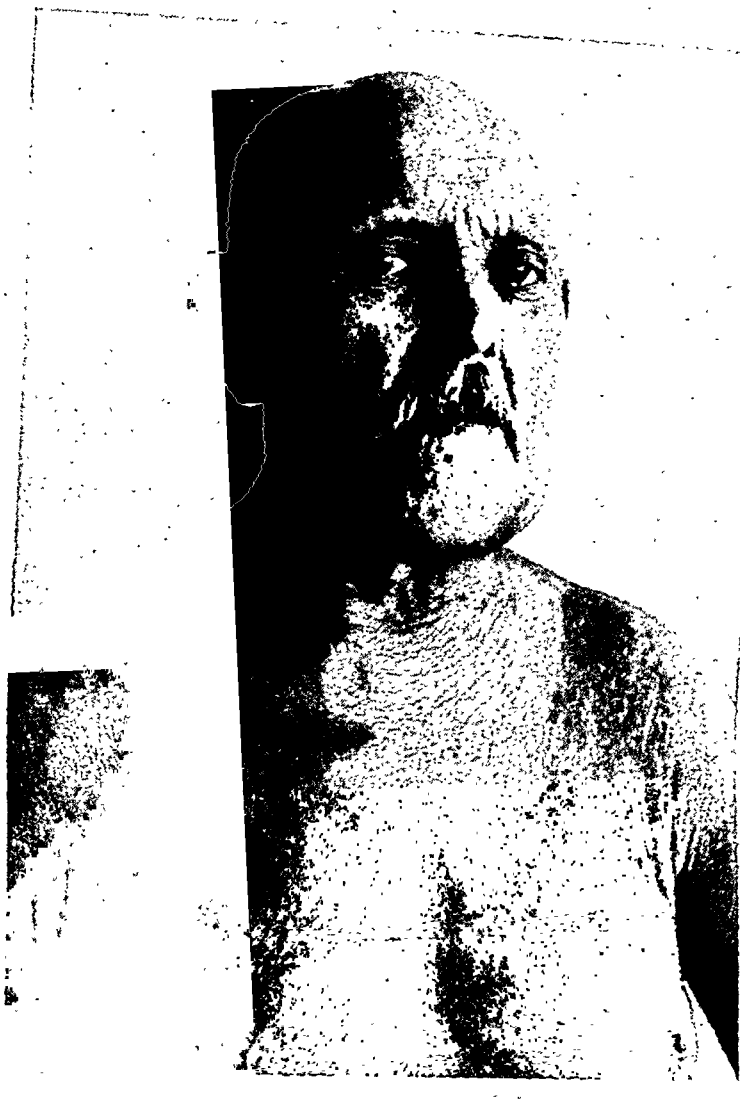


Bild 1.

Eine histologische Diagnose haben wir nicht. Das Bild entspricht demjenigen, das bei Erythrodermien gefunden wird. —

Betreffs des internen Zustandes sei Folgendes bemerkt: Ausser über seine Hauterkrankung klagte der Patient seit etwa einem halben Jahre über Kurzatmigkeit bei Anstrengung, geschwollene Beine, abends, und nachts auftretende Anfälle von Benommenheit und 3—4 maliges Harnen während der Nacht. Der behandelnde Hausarzt fand bei ihm eine Herzvergrösserung, aber normalen Blutdruck und auch keine Abweichungen im Harn, ausser leichter Albuminurie.

Diese Erscheinungen leichter Dekompensation reagierten günstig auf salzlose Diät und Verabfolgung von Digitalis. Während des Verbleibs im Krankenhause ergab sich, dass das Herz in allen Richtungen etwas zu gross



Bild 2.

war, aber keine deutlichen Dekompensationserscheinungen zeigte; die Herztöne waren normal. Leber und Milz waren nicht palpabel; der Blutdruck war, nach Spengler, 145/80; Eiweiss fand sich in Spuren; die Reduktion war negativ, Urobilin stark positiv, und im Sediment wurde sporadisch ein Leukocyt angetroffen. Die Senkungsgeschwindigkeit betrug in der 1.Stunde (nach Westergren) 37 mm, der Ureumgehalt (nach Ambard 750 mg/L.), die Anzahl Leukocyten 16,200, bei Differenzierung 3 stabförmige, 25 segmentförmige, 24 Lymphocyten, 8 Monocyten und 49 eosinophile; toxische Körnung der Granulocyten schwach positiv.

Bei der Röntgenuntersuchung des Thorax erwies sich das Herz in der Tat in allen Richtungen mässig vergrössert. In den Lungenfeldern sind keine Abweichungen und keine Schwellung der mediastinalen Lymphdrüsen sichtbar.

Während der Verpflegung schwankte die Pulsfrequenz zwischen 70 und 80 Schlägen in der Minute, die Temperatur (rektal) zwischen 36.6° und 37.5°.

Der klinische Aspekt des Patienten führte uns dazu, während der ersten Untersuchung an erster Stelle an ein Lymphogranuloma malignum zu denken, welche Krankheit ja von einer Erythrodermie begleitet sein kann. Das morphologische Blutbild, soweit dieses diagnostisch verwendet werden kann, enthielt einen Ein-

gerzeig in dieser Richtung (hohe Eosinophilie); aber das Fehlen von Fieber (wobei jedoch die kurze Beobachtungszeit berücksichtigt werden muss), die relative mässige Erhöhung der Senkungsgeschwindigkeit und die fehlende Linksverschiebung bei Differenzierung der Granulozyten schienen nicht ganz in das Bild der vorläufigen Diagnose zu passen. Um zu einer sicheren Diagnose zu gelangen, wurde zur Extirpation einer Lymphdrüse übergegangen.

Das histologische Bild der Lymphdrüse war folgendes:

Die normale Struktur einer Lymphdrüse war bei der extirpierten fast überall grossenteils verschwunden. An der Peripherie findet man grosse und kleinere Felder eines hellgefärbten Gewebes (Bild 2). Dieses ist mässig zellreich und aus Zellen mit ovalem, bisweilen spindelförmigem, aber auch wohl rundem Kerne aufgebaut. Es wird ziemlich viel faseriger und mitunter auch etwas körniger Zwischenstoff angetroffen. In diesem Gewebe findet sich ein mässiges Infiltrat von Lymphocyten, Plasmazellen und eosinophilen Zellen. Diese Felder blassen Gewebes sind durch Streifen normales Lymphdrüsengewebe, in welchem noch ziemlich viele Keimzentren bemerkbar sind, voneinander getrennt. In diesem lymphoiden Gewebe werden ziemlich viele eosinophile und Plasmazellen wahrgenommen. An den Rändern der blassen Felder, aber auch wohl in dem lymphoiden Gewebe werden recht viele Zellen beobachtet, die mit braunem Pigment beladen sind, das Melaninreaktionen ergibt und ferner eine Anzahl Zellen, die vakuolares Plasma aufweisen. In diesen Vakuolen findet sich ein Stoff, der sich mit Sudan III rot färbt.

In den retikulinen Färbungen nach Laguesse werden in den blassen Feldern nur wenig retikuline Fasern gesehen, jedenfalls weniger als in den dazwischen liegenden Streifen lymphoiden Gewebes. In der Bindegewebsfärbung nach Masson färbt sich der Zwischenstoff der blassen Felder zwar etwas bläulich, aber blaue Fasern sind nicht darin sichtbar. Die Trichromfärbungen nach Masson ergeben keine neuen Gesichtspunkte. Es liegt hier somit ein völlig typisches Beispiel der *sog. réticulose lipomélanique* (*Pautrier und Woringer*) vor.

Es handelte sich hier mithin um ein typisches Beispiel der *Réticulose lipomélanique* (Pautrier und Woringer). Wie schon in der Einleitung gesagt wurde, kommt diese Art Drüsenschwellungen bei den verschiedensten Arten von Erythrodermie vor. Hierdurch wurde das wesentlichste Argument zugunsten der Diagnose Lymphogranuloma malignum hinfällig und gewannen einige Tatsachen, welche während der Beobachtung zutage gefördert waren und nicht ganz mit der gestellten Diagnose in Einklang gebracht werden konnten, an Bedeutung, sodass von der Diagnose Morbus Hodgkin

abgesehen werden konnte. — In der Tat zeigte sich bei einer langen Nachbeobachtung nichts von dem Bestehen eines malignen Granuloms und trat unter der nunmehr gewählten Behandlung Besserung im Zustande der Haut ein, wobei auch die Lymphdrüsenschwellungen grossenteils zurückgingen. Der Patient starb 1 ½ Jahr später an seinem Herzleiden.

## Zusammenfassung.

Es wird ein Patient mit einer heftig juckenden chronischen Erythrodermie, feinschilferiger, sepiafarbig bis kupferbraun verfärbter, verdickter Haut, Haarausfall usw. beschrieben, welche Symptome mit Lymphdrüsenschwellungen und dem Vorkommen von Lymphdrüsenpaketen verbunden waren. Das histologische Bild einer dieser Lymphdrüsen zeigte das typische Bild der *Réticulose lipomélanique* (Pautrier und Woringer). Hierdurch gewannen einige klinische und Laboratoriumsdaten, die nicht mit der anfangs gestellten Diagnose in Einklang gebracht werden konnten, an Bedeutung und konnte auf die Diagnose Morbus Hodgkin verzichtet werden.

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From Ullevaal Hospital, Medical Unit VIII, Oslo.
Physician-in-chief: Dr. med. Carl Müller.

# The Electrocardiogram of Acute Hemorrhage from Stomach and Intestines.[1])

By

H. RASMUSSEN and M. FOSS.

(Submitted for publication December 29, 1941).

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During the last 10 or 15 years quite a large amount of literature has been published respecting electrocardiographic changes in cases of anemia. These publications are characterized by considerable disagreement as regards the frequency and importance of such abnormalities in the electrocardiogram recorded in anemic conditions. On the one hand, several authors have observed considerable and frequent alterations in the electrocardiogram, while many others, on the contrary, find such changes to be rare and inconspicuous.

Among 88 patients with anemia Bloch (4) found in 47 cases electrocardiographic changes, chiefly in the ST line and T wave. Zimmermann (15) found similar changes in 17 out of 36 patients with anemia, and more frequently in secondary than in pernicious anemia. Jervell and Evensen (8) observed similar abnormalities in 15 out of 26 persons with anemia and normal cardiovascular system. Among 35 patients with pernicious anemia Parade and Franke (11) found electrocardiographic abnormalities in 31.4 per cent, while the frequency in 27 cases of hypochromic anemia was 25.8 per cent.

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[1] The principal observations were reported in det Norske Medicinske Selskap on March 19th 1941 under the title: »Blødningselektrokardiogrammet» (The Electrocardiogram of Acute Hemorrhage).

On the other hand, Hochrein and Matthes (7) among 32 anemic patients under 50 years old found 8 abnormal electrocardiograms, 5 of which were seen in patients with heart disease. In two of the remaining three patients the only abnormality was a deep $Q_{III}$. They note especially that in 13 patients with severe anemia (hemoglobin below 30 per cent) normal electrocardiograms were seen. Among 44 patients Ellis (5) detected »no serious abnormalities». Misske and Otto (9) examined 182 patients with primary and secondary anemia and for the most part noted only abnormalities ascribable to degenerative changes in the cardiovascular system due to age. Only »in a very small percentage of the cases» did they find some ST and T changes. They are in agreement with Hochrein and Matthes and conclude by saying that even severe cases of anemia do not usually present signs of coronary insufficiency, either as subjective symptoms or in the electrocardiogram. Likewise Veso (14) after investigation of 30 anemic patients, came to the conclusion that anemia, even when severe, of itself produced only insignificant electrocardiographic abnormalities.

The results of the investigation which will here be reported where the electrocardiogram of acute hemorrhage is described as a separate electrocardiographic syndrome, seem well suited to clear away a great deal of this disagreement respecting the changes that may be found in the electrocardiogram of anemia. In order to emphasize this point of view fig. 1 is presented, where on the left side (a) is seen the normal electrocardiogram from an elderly woman with severe pernicious anemia and on the right side (b) the electrocardiogram from a young man who had hematemesis, but insignificant anemia. This latter electrocardiogram has negative T waves in lead I, II and IV (IVR).

It was the electrocardiogram with quickly disappearing inversions of the T wave, obtained from this young man with a normal heart, that gave the impulse to a systematic investigation of the electrocardiographic changes appearing during acute gastrointestinal hemorrhage, hematemesis and melaena. In the eleven months from March 1940 to January 1941 inclusive 45 cases of hematemesis and melaena were treated in Ullevaal Hospital, Medical Unit VIII, and all of them were investigated electrocardiographically. Owing to circumstances the interest for these matters was very small during several months, so that 14 of the 24

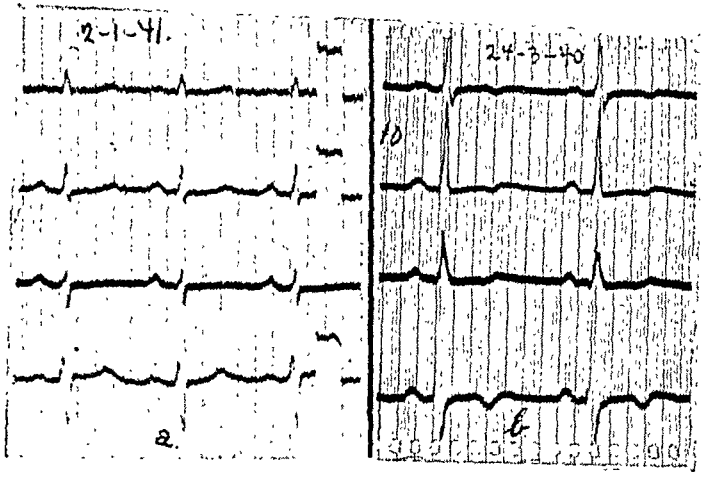



Fig. 1.

a. H. B. Female. 77 years. Pernicious anemia. Hemoglobin 35 per cent.

b. G. I. Male. 24 years. Hematemesis. Hemoglobin 83 per cent.

patients with entirely normal electrocardiograms were examined only *once*. To this main material of 45 cases comes a supplementary material of 13 cases, assembled in the 7 months from February to August 1941. These latter cases have been used especially for the study of the pathogenesis of the abnormalities.

As regards the technique it shall only be mentioned that the determination of hemoglobin was effected by means of a hemoglobinometer (Sahli *method*), adjusted to the Haldane's standard (13.8 g hemoglobin or 18.5 volume per cent $O_2$-capacity = 100 per cent).

As is known, it is often difficult to draw the line between the acute gastro-intestinal hemorrhages and the more chronic, slowly oozing forms of bleeding. Two, perhaps three patients, who showed normal electrocardiograms had such protracted hemorrhages. Some of the patients were admitted to the hospital a rather long time after the bleeding began. Thus in the case of 3 of the 21 patients with electrocardiographic changes the first electrocardiogram was not taken until 72 hours after the hemorrhage, while among the 24 without such changes there were 9 whose first electrocardiogram was not taken until 72 hours after beginning of the bleeding. As regards the site of the hemorrhage there were two cases of cancer of the stomach, one case of bleeding from oesophageal varices due to

cirrhosis of the liver, and one hemorrhage from a jejunal ulcer, verified on subsequent operation, and one hemorrhage from an ulcer in the diverticulum of Meckel also verified on operation. As to the other hemorrhages, roentgenograms taken after 4 or 5 weeks' dietary treatment sometimes revealed an ulcer, sometimes not, and the hemorrhages were presumed to be due to gastroduodenal ulcers (healed or not) or to hemorrhagic gastritis.

In 21 of the 45 patients, i. e. *46 per cent*, electrocardiographic changes were found during or after the hemorrhage. If we include the supplementary material, consisting of 13 patients, of whom no less than 12 had electrocardiographic abnormalities, we have 33 patients out of 58, so that the frequency of the electrocardiogram of hemorrhage was about *57 per cent*. In the main body of material 9 out of 13 women and 12 out of 32 men showed electrocardiographic abnormalities (Table 1).

**Table 1.**

Electrocardiographic changes in 45 patients with melaena and hematemesis.

| | |
|---|---|
| Total material: 45 patients. | 13 women and 32 men. |
| With melæna: 17 patients. | Age from 15 to 82 years. |
| With hematemesis: 28 patients. | Mean age 47 years. |

| With electrocardiographic changes: | Without electrocardiographic changes: |
|---|---|
| 21 patients or 46 per cent. | 24 patients or 54 per cent. |
| 9 women and 12 men. | 4 women and 20 men. |
| Age from 15 to 64 years. | Age from 27 to 82 years. |
| Mean age 46.5 years. | Mean age 48 years. |
| Average of lowest hemoglobin values in all cases: 54 per cent. | Average of lowest hemoglobin values in all cases: 62 per cent. |

Among the 21 patients with electrocardiographic changes 17 have an absolutely pathological electrocardiogram, when the usual criteria for judgement are applied (ST line lowered 1 mm or more below the isoelectric line in one or more leads, T wave flattened to 1 mm or lower, isoelectric or negative in lead I or II). Four patients had an electrocardiogram which, taken alone, must no doubt be regarded as normal, but which on subsequent control examinations proved to differ from the patient's normal electrocardiogram. For instance, a negative $T_{III}$ might afterwards become positive.

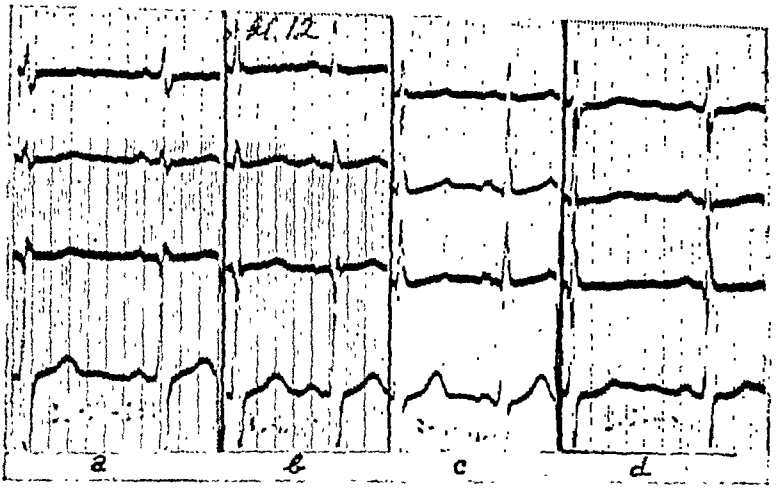



Fig. 2.

a. N. K. Male. 35 years. Hemoglobin 102 per cent.
b. A. D. Female. 48 years. Hemoglobin 60 per cent.
c. I. R. Female. 53 years. Hemoglobin 65 per cent.
d. E. H. Female. 41 years. Hemoglobin 60 per cent.

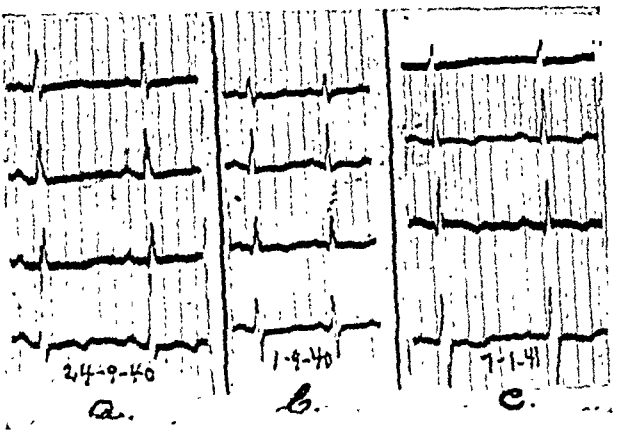



Fig. 3.

a. Aa. R. Female. 49 years. Hemoglobin 87 per cent.
b. O. J. Male. 78 years. Hemoglobin 20 per cent.
c. H. J. Male. 49 years. Hemoglobin 14 per cent.

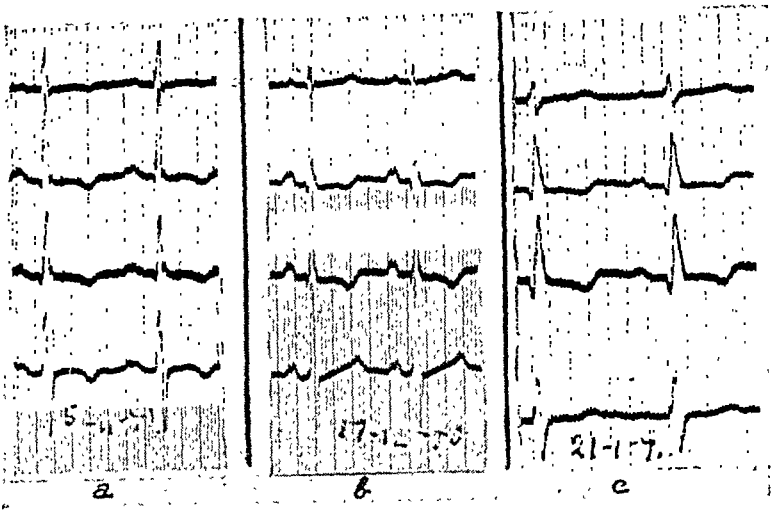


Fig. 4.

a. R. L. Female. 38 years. Hemoglobin 78 per cent.

b. R. M. Female. 36 years. Hemoglobin 73 per cent.

c. G. G. Male. 42 years. Hemoglobin 53 per cent.

The characteristic changes observed during gastro-intestinal hemorrhage have practically all occurred in the ST interval and the T waves (Figs. 2, 3 and 4). Fig 2 shows the minor degrees of these changes, Fig. 3 the more pronounced abnormalities with T wave inversions, while Fig. 4 shows the greatest abnormalities with depression of the ST line. The depression of the ST line occurs primarily in the 2nd and 3rd leads. Most frequent and especially noticeable is the alteration in the form of the T waves, which sometimes become more flattened, sometimes isoelectric and sometimes negative in one, two, three or all four leads. In the slighter hemorrhages, and as a stage in the reversion to normal in the more severe cases, a rather characteristic picture is obtained, where the ST line, starting under the isoelectric line, runs obliquely upwards to the T wave, which is not clearly marked off from the ST interval. The T wave then rises to a small peak, instead of having the usual evenly rounded form, and thus acquires a tentlike appearance (Fig. 2c). The changes in the T wave occurred perhaps most frequently in the 2nd and 3rd leads, but they were not seldom seen in the first lead and somewhat more rarely in the fourth (IV R). In some of the patients all the T waves were inverted (Fig. 4 a). That the changes here mentioned are merely stages of one and the same develop-

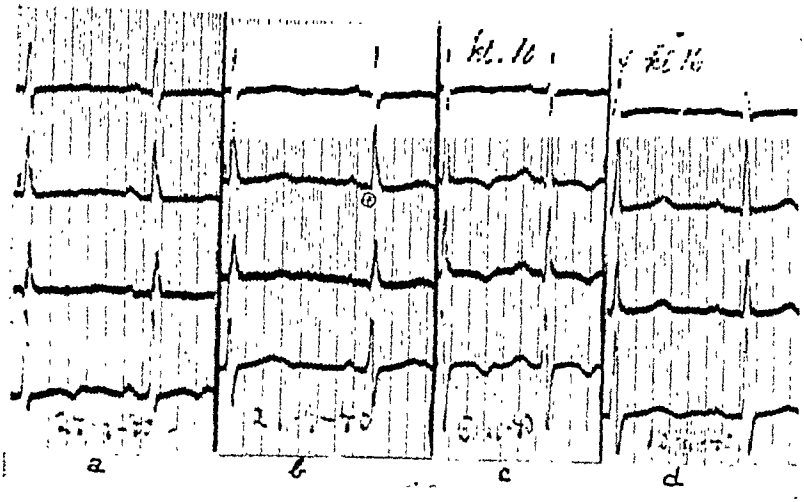


Fig. 5.

*a and b.* Aa. R. Female. 49 years.
a. 2 days after hemorrhage.
Hemoglobin 87 per cent. B. P. 110/70 mm.
b. 6 days after hemorrhage.
Hemoglobin 68 per cent. B. P. 110/70 mm.
*c. and d.* R. L. Female. 38 years.
c. 5 days after hemorrhage.
Hemoglobin 78 per cent. B. P. 140/85 mm.
d. 10 days after hemorrhage.
Hemoglobin 57 per cent. B. P. 115/60 mm.

ment is seen from the fact that several of the patients, who at first presented great electrocardiographic abnormalities, afterwards when getting better, but before the electrocardiogram became quite normal, presented some of the slighter changes. The T waves, which at first were inverted, became isoelectric, then slightly positive, perhaps tent-shaped, and finally acquired the normal appearance and height. The electrocardiogram became normal after some time in all cases except two, where $T_I$ remained isoelectric during the whole period of observation, 6 or 8 weeks. One of these patients, however, also had a pulmonary embolism during treatment in bed (Fig. 5, c and d).

No abnormalities were found in the QRS complex, apart from a transient $Q_{III}$ in one patient. Neither did the P waves show any distinct changes during the hemorrhage or subsequently. In the pathological electrocardiograms they are not particularly high, never above 3 mm, and as a rule they do not afterwards decrease in height. In some few cases the P waves showed a slight tendency to

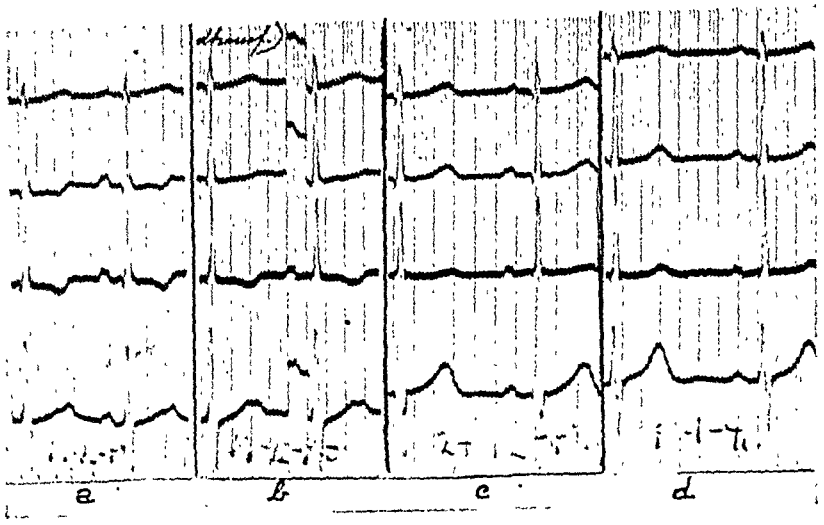



Fig. 6.

*a, b, c and d:* R. M. Female. 36 years.
a. 2 days after hemorrhage.
Hemoglobin 73 per cent. B. P. 90/65 mm.
b. 3 days after hemorrhage.
Hemoglobin 40 per cent. B. P. 125/60 mm.
c. 9 days after hemorrhage.
Hemoglobin 49 per cent.
d. 33 days after hemorrhage.
Hemoglobin 83 per cent. B. P. 100/70 mm.

diminish during the period of observation, for example by 1 or 2 mm, but in some other cases they rose in corresponding degree according as the electrocardiogram became normal. In the electrocardiograms taken during acute hemorrhage, in a state of shock, considerable tachycardia was often present, but as a rule the increase in frequency was small compared with the subsequent control electrocardiograms, so that the rise in frequency is certainly in itself without importance as regards the occurrence of the abnormalities (Fig. 5 and 6).

In 16 patients the abnormalities were found in the first electrocardiogram, in 3 cases in the second, while in 2 cases they appeared later. In 8 patients they were observed on the first day, at the earliest after about 12 hours, in 3 on the second, in 4 on the third day, in 6 from the fifth day onwards. As the electrocardiograms recorded after admission were taken at intervals of 3 or 4 days, the time of disappearance of the abnormalities has not been quite accurately established, and the periods of duration stated represent minimum figures. While only one electrocardiogram was taken

from some of the patients, the abnormalities in 6 patients lasted four days or less, in 7 of them from 5 to 9 days, in 4 from 10 to 20 days and in one case for 30 days.

Symptoms from the heart during and after the hemorrhage seldom occurred, probably because the patients were strictly confined to bed. One woman (Fig. 2 b) with slight hypertension had precordial pains, diagnosed as angina pectoris. A young man, whose electrocardiogram was normal two days after the hemorrhage, had marked dyspnea when cycling. A woman whose first electrocardiogram, taken 6 days after the hemorrhage, was abnormal, had been up and moving about, but with dyspnea and severe palpitations. It is of interest to note that syncope has occurred in 7 of the 21 patients with electrocardiographic changes and 4 of the 24 without such abnormalities.

None of the patients had heart disease. Two women had moderate hypertension, without hypertensive heart disease. Two had had rheumatic fever, but had no signs of valvular lesions and X-ray examination revealed normal hearts.

One patient, a man aged 66, died. He had an electrocardiogram, resembling the Wilson bundle branch block type, but with a QRS duration of a little more than 0.10 sec., but otherwise none of the changes which are here regarded as characteristic, and he is therefore assigned to the negative group.

Before proceeding to an examination of some of the factors which may have significance for the occurrence of this electrocardiogram of acute hemorrhage it can in general be said that the abnormalities here observed resemble those seen in cases of coronary insufficiency, for instance in attacks of angina pectoris, and those arising in myocardial ischemia, for example on breathing air poor in oxygen. They also resemble the orthostatic changes seen in the electrocardiogram, as well as those described in diabetic coma and further those observed in extrarenal hyperazotemia with dehydration. Several of these changes are regarded as being due to coronary insufficiency.

From Table 1 it appears that with respect to age the patients with the electrocardiogram of hemorrhage do not differ particularly from those with normal electrocardiogram. The percentage of changes in women is greater than in men. The average figures for minimum hemoglobin content of the blood seem to show that

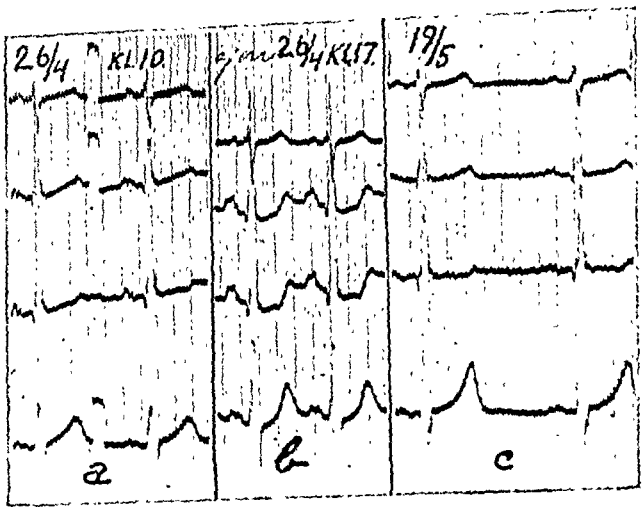



Fig. 7.

*a, b and c:* T. J. Male. 28 years.
a. The day of hemorrhage.
Hemoglobin 62 per cent. B. P. 120/65 mm.
Blood Urea 72 mg per cent.
b. The same day, 9 hours later.
Hemoglobin 55 per cent. B. P. 90/0 mm.
c. 24 days after hemorrhage.
Hemoglobin 62 per cent. B. P. 120/55 mm.
Blood Urea 31 mg per cent.

somewhat more severe hemorrhages appear in the group with an abnormal electrocardiogram.

A more searching examination shows, however, that severe hemorrhages with considerable anemia may occur without the characteristic changes. For example, the man who died had a QRS complex with a broad $S_I$, but otherwise a normal electrocardiogram. On the other hand, the characteristic picture was seen in patients with normal content of hemoglobin in the blood (see Fig. 2 a) or else only slightly reduced content (Fig. 1 b). This seems to be due partly to the hemorrhage having been so small that it did not lead to anemia, although producing changes in the electrocardiogram, partly, and more frequently, to the electrocardiogram having been recorded before the posthemorrhagic dilution of the blood and the fall in hemoglobin commenced. On further examination of the electrocardiographic findings and the concentration of hemoglobin in the individual cases it was found to be a regularly occurring phenomenon that the most pronounced changes appear at an early stage, with relatively high hemoglobin content, and that

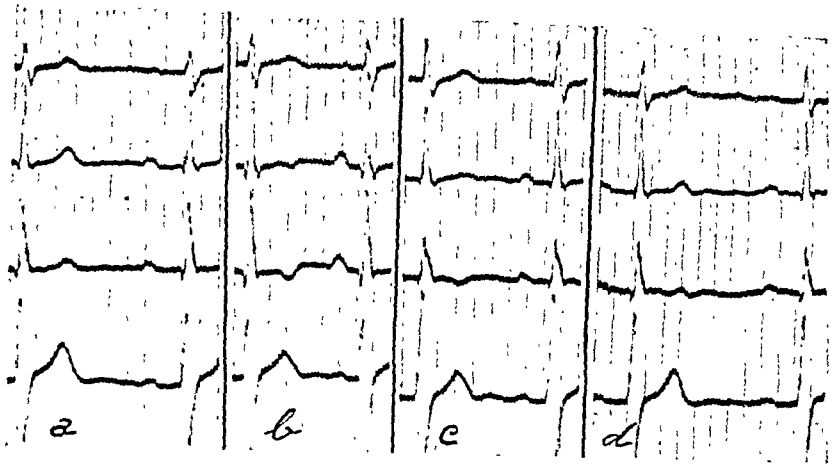



Fig. 8.

*a, b, c and d.* A. S. Male. 34 years.
a. After slight hemorrhage.
Hemoglobin 100 per cent. B. P. 120/80 mm.
*b.* New severe hemorrhage.
Hemoglobin 75 per cent. B. P. 140/70 mm.
c. One day *after last hemorrhage.*
Hemoglobin 69 per cent. B. P.?
Blood Urea 49 mg per cent.
d. 13 days after last hemorrhage.
Hemoglobin 87 per cent. B. P. 120/75 mm.
Blood Urea 38 mg per cent.

the alterations in the electrocardiogram more or less completely disappear in the following 5 or 10 days, while the hemoglobin concentration of the blood steadily decreases. The electrocardiogram becomes normal, but the anemia gets worse. The hemoglobin values and not the number of erythrocytes have been employed, as the oxygen-carrying capacity of the blood has been regarded as the essential point. This finding of a steadily improving electrocardiogram together with an increasing anemia has been made in 11 of the 21 patients with electrocardiographic abnormalities, or in 11 of the 16 cases where the examination was sufficiently detailed (Figs. 5, 6, 7 and 8). We conclude herefrom that the hemoglobin content of the blood has no significance as regards the electrocardiographic changes and that the electrocardiogram of hemorrhage is not an »electrocardiogram of anemia».

The systolic and diastolic blood pressure was as a rule found to be within normal limits. In a couple of patients a considerable fall in blood pressure was recorded during the acute stage of shock.

In one with marked symptoms of collapse and a palpatory blood pressure, systolic, of 50 mm Hg the electrocardiogram was normal, but after some time became pathological, with the characteristic abnormalities. On following up the blood pressure in the individual cases during the first weeks after the hemorrhage, it was found that both the systolic and the diastolic pressure have a tendency to fall, while at the same time the electrocardiogram becomes normal. Such a contrast in the development, a reduction in blood pressure together with an improving electrocardiogram, has been seen in 8 of the 10 patients who were studied in sufficient detail (Fig. 5, 6, 7 and 8). Thus a fall in blood pressure is not the cause of the electrocardiogram of hemorrhage. On the contrary, the findings point rather to a reactive rise in blood pressure during the acute hemorrhage.

We have not made investigations respecting the behaviour of the total blood volume, the cell volume and the plasma volume in relation to the occurrence of the electrocardiogram of hemorrhage. Such investigations have been made by Bennet, Dow, Lee Lander and Wright (3) in a number of cases of gastrointestinal hemorrhage. They find that the plasma volume is re-established very rapidly by absorption of liquid from the tissues, mostly in some few hours, though it sometimes takes 24 hours. But as the cell volume still remains reduced, the total blood volume continues to be lower than normal. The total blood volume is not regained until the blood corpuscles are regenerated, i. e. after 3 to 6 weeks. Compared herewith, the electrocardiographic changes persist long after the plasma volume is restored, but as a rule they have disappeared long before the time when the total blood volume should be re-established. It may here be mentioned that our patients received about 2000 $cm^3$ of liquid perorally from the first day of treatment, to which comes eventual intravenous or intrarectal administration of liquids. On 12 occasions the effect of transfusion of blood (500 $cm^3$) was investigated. In 3 cases the electrocardiographic abnormalities became less prominent, in 7 they remained unchanged, while in 2 cases they were more marked.

Some few incidental observations, made in the main material respecting the relation of the extrarenal hyperazotemia during hemorrhage to the electrocardiogram of hemorrhage, led us to look a little more closely into this matter in the supplementary material,

consisting of 13 patients. For determination of the blood urea we employ a gasometric method, cf. Van Slyke, Page, Hiller and Kirk (13). The upper normal limit is found to lie between 40 and 50 mg per cent.

In the total material consisting of 58 patients 33 show electrocardiographic abnormalities and 23 of these have a blood urea content of more than 40 mg per cent, while 16 have above 50 mg per cent. Of the 58 patients 29 have hyperazotemia exceeding 40 mg per cent and 23 of them have electrocardiographic abnormalities. Hyperazotemia above 50 mg per cent was found in 20 patients, of whom 16 had abnormalities in the electrocardiogram. One of the 4 without abnormalities was the patient who died. On examining the course of the hyperazotemia and the electrocardiogram of hemorrhage in one and the same patient we find no slight degree of concordance between the hyperazotemia and the electrocardiographic changes. This is illustrated in Chart 1 as regards 5 patients, while sufficient data are available for 8 or 9 patients.

Of 5 patients with hyperazotemia four had normal serum chloride, determined by the usual Volhard titration after open Carius digestion (Van Slyke), while one showed a slight reduction, 97 m. eqv.

It is fairly obvious that it is not a question of an effect of the hyperazotemia itself upon the electrocardiogram. Nevertheless we have inspected electrocardiograms from 10 patients with severe chronic hyperazotemia due to renal insufficiency, and none of them showed abnormalities of the type here described. It is natural to regard both phenomena as results of one and the same disturbance, and then especially as a result of the circulatory failure, which occurs in acute hemorrhage, cf. the symptoms of syncope. A few cases of similar electrocardiographic changes in cases of dehydration and extrarenal hyperazotemia are described by Gömöri and Gruber (6), who have also produced them experimentally in cats by means of dehydration. They discuss, among other possibilities, the question of a direct dehydration of the cardiac muscle as the cause. The electrocardiographic abnormalities in diabetic coma with dehydration and hyperazotemia may perhaps be regarded from the same standpoint, see, for instance, Aschenbrenner (2), who, however, considers the administration of insulin to be the essential factor.

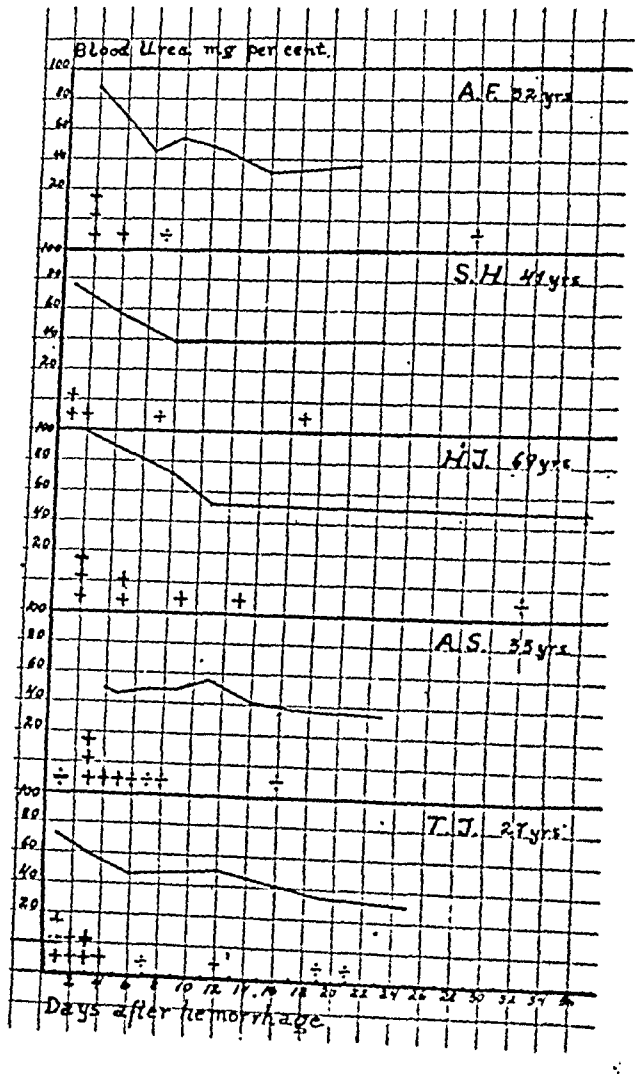



Chart 1.

Blood Urea and electrocardiographic changes after hemorrhage

Pronounced electrocardiographic changes: .. + + +

Moderate electrocardiographic changes: .... + +

Slight electrocardiographic changes: ..... +

No electrocardiographicchanges: ..... ÷

Distinct signs of dehydration were present in some of our patients, who have also presented considerable electrocardiographic abnormalitites. Most of them, however, showed no definite sign of dehydration and the supply of liquids during the treatment was relatively copious.

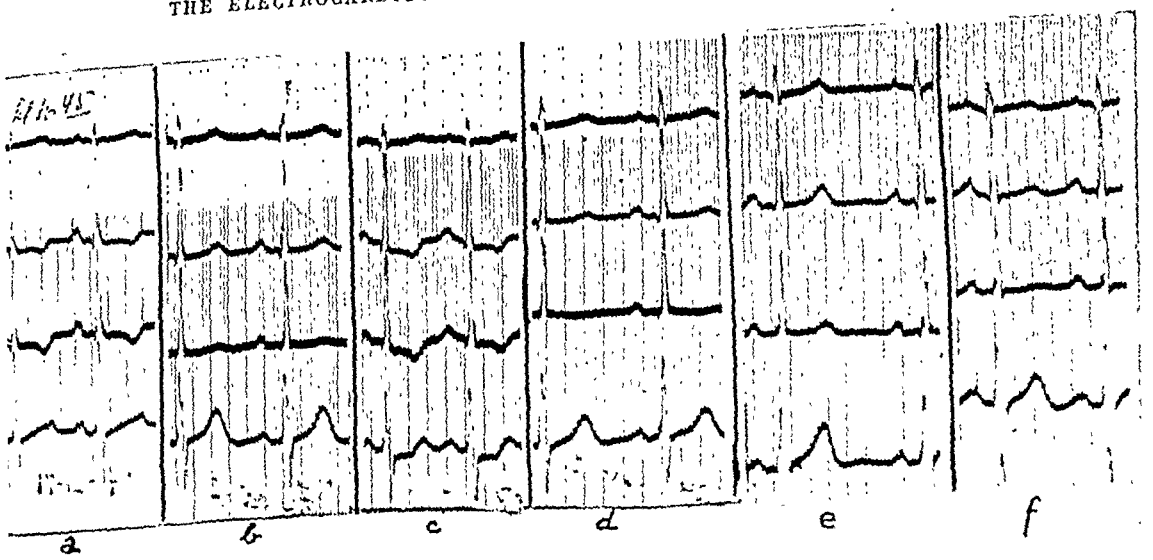



Fig. 9.

*a, b, c, d, e and f:* R. M. Female. 36 years.
a. 2 days after hemorrhage.
Hemoglobin 64 per cent. B. P. 90/65 mm.
*b, c, and d:* 15 days after hemorrhage, anoxemia produced by breathing air with gradually reduced oxygen tension.
b. Control electrocardiogram.
Hemoglobin 53 per cent. B. P. 100/60 mm.
c. Maximal anoxemia.
d. After 5 minutes of open air breathing.
*e and f:* 85 days after hemorrhage. Anoxemia function test.
e. Control electrocardiogram.
Hemoglobin 111 per cent. B. P. 115/80 mm.
f. Maximal anoxemia.

new evidence, sufficient to justify the acceptance of his opposite view.

In order further to investigate the question whether the electrocardiogram of hemorrhage is really due to myocardial anoxemia, we made anoxemia experiments on some patients whose electrocardiogram had shown abnormalities after hemorrhage but had just become normal again. Anoxemia was induced by letting the patient breathe in the Krogh apparatus for determination of the basal metabolism, filled with atmospheric air, so that the oxygen tension gradually diminished during the breathing. In 16 normal individuals, 8 men and 8 women, considerable cyanosis arose after respiration for 8, 10 or 12 minutes and the experiment was then discontinued. Slight flattening of the T waves and very slight depression of the ST interval were noted. In R. M., a woman aged

36, whose electrocardiogram showed great abnormalities during the gastric hemorrhage (Fig. 6), such an anoxemia test 15 days after the hemorrhage produced exactly the same electrocardiographic picture (Fig. 9) as she had had during the hemorrhage. As is seen from Fig. 9, her electrocardiogram before this test was not altogether normal (isoelectric $T_{III}$) and her hemoglobin was low, 53 per cent. But exactly the same results were attained in anoxemia tests 30 days and 54 days after the hemorrhage, when she had a hemoglobin content in the blood of respectively 89 per cent (with 4,500,000 red blood corpuscles) and 95 per cent. $T_{III}$ was then on both occasions slightly positive. The curves from these tests are not reproduced here. 85 days after the hemorrhage, when she had a hemoglobin content of 111 per cent and a high $T_{III}$, she reacted to the anoxemia test with the slight changes seen in Fig. 9, e and f, which corresponds to a normal reaction, such as was found in the 16 normal individuals. Fifteen days later, or 100 days after the hemorrhage, when the hemoglobin content was 100 per cent, she reacted to the test in exactly the same manner. We shall refrain from speculations respecting this increased susceptibility of the myocardium to anoxemia, a susceptibility persisting for at least 54 days after the hemorrhage.

These experiments seem to furnish strong support for the view that the electrocardiogram of hemorrhage is a manifestation of myocardial anoxemia and thereby also for the assumption of a coronary spasm as the cause.

The hemorrhages which evoked these electrocardiographic abnormalities had their origin chiefly from the stomach and duodenum, being due to ulcer or gastritis and in two cases to cancer. Three of the hemorrhages were from other sources, the cause being in one case oesophageal varices, in another jejunal ulcer and in a third ulcer in the diverticulum of Meckel. It was deemed to be of great importance to ascertain whether also other acute hemorrhages called forth the same changes in the electrocardiogram. With the kind permission of Professor Sunde we have examined in the University Obstetric Clinic of Oslo 6 women with puerperal hemorrhage. Their ages varied from 19 to 40 years, the quantity of blood lost was from 1200 to 1300 $cm^3$ and the lowest hemoglobin values ranged from 54 to 88 per cent. Some of the patients were probably anemic before delivery. None of these six women had the charac-

undoubtedly belongs to it and with equal certainty one of Veso's cases (14). These authors, as well as others studying the electrocardiogram in anemia, are now and then struck by the incongruity between the electrocardiographic anomalies and the anemia in some of their cases.

The recognition of the syndrome of the electrocardiogram of hemorrhage seems to a large extent to clear away the disagreement between the group of authors who find »anemia electrocardiograms» to be a frequent occurrence and those who find them to be rare. When Hochrein and Matthes (7), for example, find very few electrocardiographic changes in anemia, the obvious reason is that they include only cases of anemia which have lasted for 3 months, a space of time which according to Büchner is necessary for the development of morphological effects of coronary insufficiency, and that they exclude all hemorrhages due to ulcer, as these patients have a special »vegetative stigmatisation».

A clinical analysis of the material was undertaken in order to try to get an idea of the mechanism of the electrocardiogram of hemorrhage. It has been established that it is not due to anemia. This is clear from the fact that it has been found where no anemia existed, as well as from the fact that the abnormalities disappear at the same time as the anemia increases owing to the posthemorrhagic fall in hemoglobin. This latter phenomenon has been the rule. Neither is a fall in blood pressure the cause of the phenomena, as the blood pressure, both systolic and diastolic, is rather higher in the period with ST—T changes than later on, when the electrocardiogram has become normal. The electrocardiogram of hemorrhage persists for a longer time than the fall in plasma volume, cf. Bennet and associates (3), but mostly for a shorter time than the fall in cell volume and consequently in the total blood volume. There seems to exist a fairly close correlation between the occurrence of abnormalities in the electrocardiogram and the appearance of the extrarenal hyperazotemia which often accompanies melaena and hematemesis, even though such anomalies may also occur without hyperazotemia. Although only a few of these patients showed definite signs of dehydration, we are led to think of similar functional anomalies in the electrocardiogram which have been observed in case of dehydration with acute circulatory failure and consequent extrarenal hyperazotemia. There is likewise here indicated a connection with

the electrocardiographic abnormalities seen in diabetic coma, where dehydration, acute circulatory failure and extrarenal hyperazotemia are commonly present. In these conditions, however, not only is the blood volume reduced, but there is also a fall in blood pressure and diminished velocity of blood flow.

It is to be noted that the electrocardiographic abnormalities in acute hemorrhage resemble those seen in myocardial anoxemia. The assumption that myocardial anoxemia is really present is strongly supported by anoxemia tests on a patient who shortly after the hemorrhage had a highly pathological electrocardiogram. During the experimental anoxemia the electrocardiographic picture was exactly the same as had been observed during the hemorrhage. As this myocardial anoxemia in gastro-intestinal hemorrhage is not caused by reduced hemoglobin content of the blood or fall in blood pressure, it seems necessary to conclude that a *coronary spasm* is present. There is reason to believe that peripheral spasms of arteries and arterioles occur during acute hemorrhages, and thus also the arterial system takes part in the reduction in capacity of the vascular system which is necessitated by the fall in blood volume. These electrocardiograms of hemorrhage may thus be interpreted as objective signs of the existence of similar processes in the central part of the arterial system, namely in the arteries supplying the cardiac muscle. Only one patient who had a slight hypertension, had pains in the chest during the hemorrhage which was attended by electrocardiographic anomalies. This fact, however, does not conflict with the interpretation of the phenomena as being due to myocardial anoxemia, since very pronounced electrocardiographic changes due to anoxemia may be observed where no pains are present, for instance, in anoxemia tests on patients with anemia (in our own and other experiments). It may be questioned whether the duration of the anomalies, 1, 2 or 3 weeks, conflicts with the view that they are a manifestation of coronary spasms.

Possibly the electrocardiographic abnormalitites in case of dehydration with extrarenal hyperazotemia may be regarded in the same manner, namely as indicative of myocardial anoxemia arising in connection with coronary spasms as part of the general constriction of the arteries due to reduced blood volume. But also other factors here come into play, such as fall in blood pressure and reduced velocity of blood flow.

It was considered that it would be of considerable importance to be able to show the existence of such electrocardiograms in other acute forms of hemorrhage. In six parturient women with hemorrhages of 1200—1300 $cm^3$ no electrocardiographic anomalies were found. This negative result may be due to the too small extent of the hemorrhages and to special protective mechanisms, present in parturient women. Further investigations respecting acute external hemorrhages are desirable.

One of us (H. R.) has received financial support for this investigation from the fund »Nationalgaven til Chr. Michelsen».

## Summary.

1. On examination of 58 cases of hemorrhage from stomach and intestines it is found that electrocardiographic abnormalities frequently appear in these conditions. The anomalies are seen chiefly in the T waves, which become flattened, isoelectric or negative, but also in the ST interval, which, is found to be lowered. These changes appear in greater or lesser degree in about 50 per cent of the cases. The characteristic picture presented by these changes and their frequent occurrence justify the establishment of a new functional electrocardiographic syndrome: the electrocardiogram of acute hemorrhage.

2. It is shown that the changes are due neither to anemia nor to fall in blood pressure. A certain correlation is found between the electrocardiographic syndrome and the extrarenal hyperazotemia which accompanies these hemorrhages.

3. From the results of experiments with respiration of air with reduced $O_2$ content, whereby it was found possible to reproduce exactly the electrocardiogram of hemorrhage previously obtained from the same patient, it is deemed most probable that myocardial anoxemia is the cause of the electrocardiographic changes. As anemia and fall in blood pressure are without significance, it is concluded that the myocardial anoxemia is due to coronary spasm, as part of a general spasm of arteries and arterioles resulting from the sudden reduction in blood volume.

4. It is found probable that a large number of the electrocardio-

graphic abnormalities which various authors have observed in anemia, are due to acute hemorrhage and not to the anemia.

5. The importance of a knowledge of the electrocardiogram of hemorrhage with respect to the differential diagnosis of abnormalities of the ST interval and T wave is obvious.

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# The interpretation and significance of the various types of gallop rhythm.

By

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In gallop rhythm an extra sound, the so-called gallop sound, is heard in addition to the two ordinary heart sounds. In the case of rapid heart-action the ear cannot perceive the particular point in the pulse period where this gallop rhythm occurs. This may also apply to normal frequency. A further difficulty is met with in deciding whether a gallop sound or a duplication of the first or second heart sound is actually present. Phonocardiography makes this differentiation possible. An extensive phonocardiographic literature is available. A good summary will be found in the monograph by Orias and Braun-Menendez (11), »The Heart Sounds in Normal and Pathological Conditions», which was published in 1939.

In the normal phonocardiogram a third heart sound and an auricular sound are found besides the first and second heart sound. This applies to children as well as to adults.

*The third heart sound* (Figures 2, 3, 4 and 5) sets in 0.11—0.15 seconds after the beginning of the second sound. In english and american literature this period is usually called »the phase of rapid filling». As shown by Ohm in 1930 (10) the third sound depends on the blood rushing in and colliding with the ventricular wall, when during diastole the difference in pressure between the auricle and the ventricle is at its highest. Normally the third heart sound is of such a low frequency (the number of vibrations being below 40 cycles per second) as to be inaudible. In the case of ventricular dila-

tation the difference in pressure is increased, the collision with the ventricular well becomes stronger, the amplitude and frequency of the sound grows, all of which contributes towards rendering the third heart sound audible. Such a *third sound gallop or protodiastolic gallop* (Figures 3, 4 and 5) is no rare occurrence, appearing, in various types of myocardial damage. Generally the third gallop rhythm is benign. It is of particular assistence in recognizing myocardial weakness.

*The auricular sound* (Figures 2, 6 and 7) occurs in presystole on an average 0.07 seconds before the beginning of the first heart sound and 0.12 seconds after the beginning of the P wave in the electrocardiogram. It is a function of auricular work. The existence of this sound in normal and pathologic conditions has repeatedly been proved. In cases of complete block it has been registered in connection with the P wave in the electrocardiogram. It always disappears in cases of auricular fibrillation.

The auricular sound can be registered normally in a great number of all individuals though it is not quite so common as the third sound. Like the third sound it is inaudible in ordinary auscultation owing to its low frequency. In auricular dilatation the amplitude and frequency of the auricular sound increase, resulting in an *auricular sound gallop or presystolic gallop.* (Figures 6 and 7). Thus, enlarged P waves in the electrocardiogram, and auricular sound gallop, might be expected to be analogous phenomena. However, this is not always the case. I have elswhere published cases of auricular dilatation, demonstrated by x-ray, which elucidate this point. In some instances the dilatation was indicated both by the electrocardiogram and by the phonocardiogram while in other cases only one of these methods gave positive results.

Contrary to the third sound gallop, the auricular sound gallop is a grave clinical symptom. It occurs most frequently in cases of mitral stenosis with enlarged left auricle. As a rule it indicates a more or less pronounced venous congestion.

In accelerated heart rate and in prolonged conduction time the third sound approaches the auricular sound in the tracing. They may even amalgamate into a so-called *summation sound. The summation gallop* (Fig. 8) is particularly common in children with their higher heart rate. It is supposed to have the same clinical significance as the auricular sound gallop.

As regards the occurence of the different gallop rhythms Battro, Braun-Menendez and Orias (1) and Wohlferth and Margolies (15) state that the summation gallop is most common. The latter authors have published 60 cases of gallop rhythm, including 14 cases of third sound gallop, 22 of auricular sound gallop and 24 of summation sound gallop.

From the point of view of differential diagnosis some other sound phenomena may be mistaken for gallop sounds. This applies to the duplication of the first and second heart sounds. A *duplicated first sound* (Fig. 9) is not a pathologic phenomenon. One assumes that the two chief components which make up the first sound here are distinguished. These components are the muscular one appearing simultaneously with the isometric phase and the vascular component when the blood rushes out through the arerial ostia. The *duplicated second sound* (Fig. 7) also appears in physiologic conditions and is attributed to the semilunar valves not closing precisely at the same time. The phenomenon occurs regularly in bundle branch block.

A further phenomenon, usually not looked upon as belonging to the gallop rhythms, is, »*the opening snap of the mitral valve*» (Fig. 10), first described by Margolies and Wohlferth in 1932 (9) and verified by, among others, Laubry (5). It is generally regarded as a pathognomonic symptom of mitral stenosis and explained as a clicking sound, produced when the stiff mitral valves open. »The opening snap» occurs about 0.07 seconds after the beginning of the second sound.

The differential diagnosis between these three phenomena, i. e. duplicated second sound, »opening snap» and the third sound is not always easy. It is possible by means of simultaneous registration of venous pulse and phonocardiogram. The v wave in the phlebogram, appearing just after the second heart sound, is the key to the interpretation. The duplicated second sound occurs on the ascending line of the v wave, »the opening snap» simultaneously with the top of the v wave, the third sound coinciding with the descending line of the v wave. (Fig. 1).

The auscultation of the gallop rhythms is best made at the apex or further laterally. The ear must be trained to low frequency sounds. Preferably a stethoscope should be used with a »microphone», not too small.

Patients with comparatively mild cardiac symptoms such as beginning dyspnoea, slight tachycardia and fatigue, often have a second sound which is not quite distinct and which on the phonocardiogram shows a third sound. Whether this should be regarded as a normal third sound or a gallop sound is revealed, by the calibrated method. Invariably the pathologic sound posseses a greater amplitude or a higher pitch or both than the normal third sound. Often X-ray shows a dilatation of the ventricle and the electrocardio-

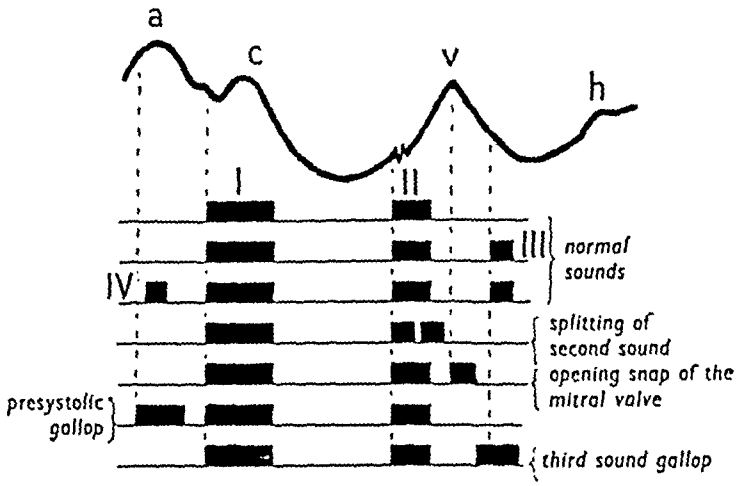



*Fig. 1. Diagram of the heart sounds and the venous pulse.*
(According to Cossio and Orias). The second component of the duplicated second sound coincides with the ascending line of the v wave. »The opening snap of the mitral valve» occurs simultaneously with the top of the v wave. The third sound appears in the descending line of the v wave.
I = the first sound. I = the second sound. III = the third sound. IV = the auricular sound.

gram more or less marked signs of myocardial damage. Real myocarditis is rare compaired with ventricular dilatation of other origin, toxic or arteriosclerotic. Earlier the »over-work» factor was much emphasized. Such patients, as a rule, may be given a small dose of digitalis. Should it be a case of a normal third sound gallop, as often, in young people, digitalis will be without effect.

The relationship between gallop sound and diastolic murmur is of interest. The over-tones of the third sound are often perceived by the ear as a protodiastolic murmur. The over-tones of the enlarged auricular sound in the presystole are heard as the presystolic murmur. Yet, a protodiastolic or presystolic murmur does not necessarily presuppose the corresponding gallop sounds. Nor

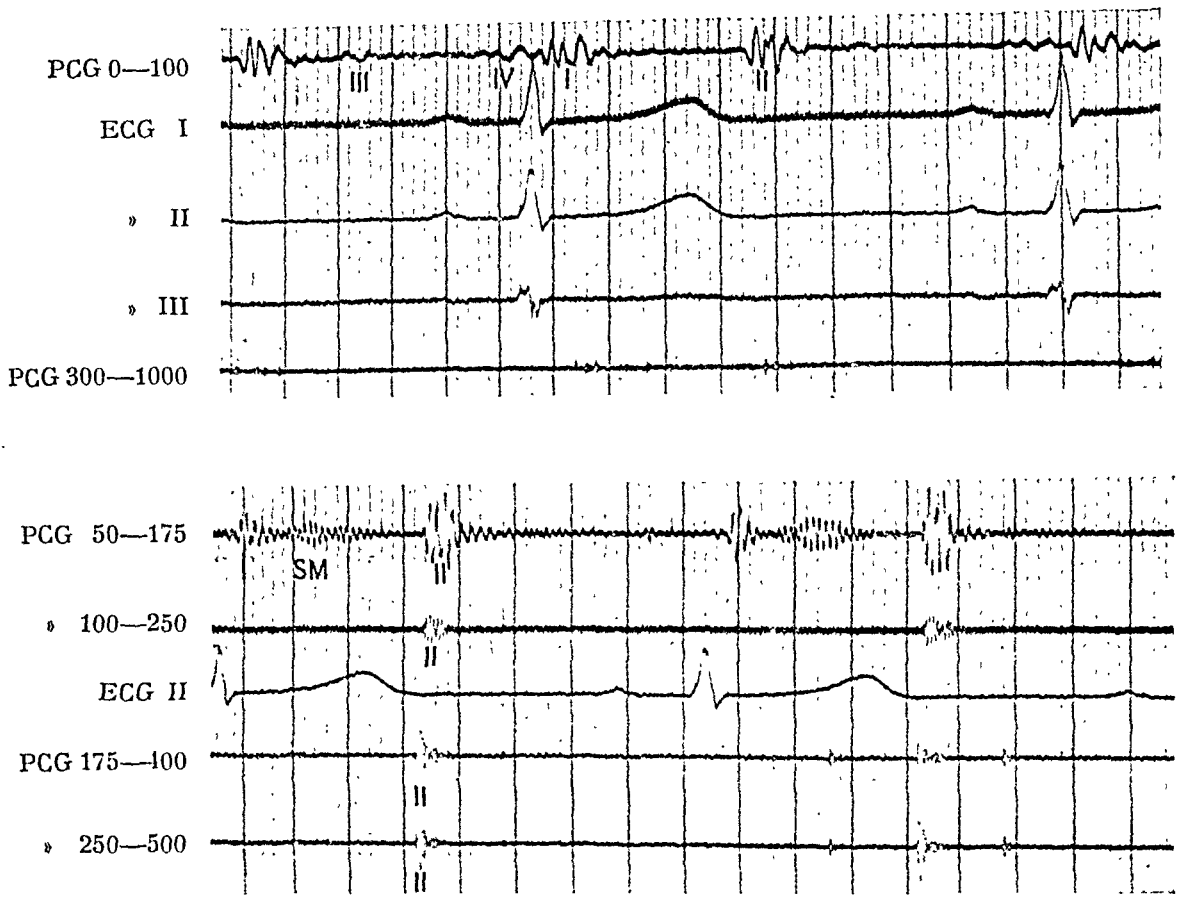
need the gallop sounds have overtones to such an extent that actual murmurs are heard. I have published a case of septic carditis and auricular sound gallop which exemplifies these points.[1] Early in the disease signs of mitral stenosis with auricular sound and presystolic murmur were present. Later, as the patient improved, the sign of stenosis, the presystolic murmur, disappeared leaving only the marked auricular sound as a sign of auricular enlargement, which also was verified roentgenologically.

The auricular sound, as well as the presystolic murmur, disappear in auricular fibrillation when the auricles do not contract.

The tracings here reproduced are mostly from patients in the IV Medical Service of St Eriks' Hospital.

Calibrated phonocardiography has been used offering the possibility of recording the strength as well as the frequency of the sounds. Previously no means existed of distinguishing, between normal sounds and gallop sounds. Calibrated phonocardiography makes this possible since absolute measurements of the amplitudes are obtained within different ranges of frequency. As regards the technical side earlier works are referred to. (6, 8).

[1] Mannheimer. Nord. Med. Vol. 12. Page 3622.1941.



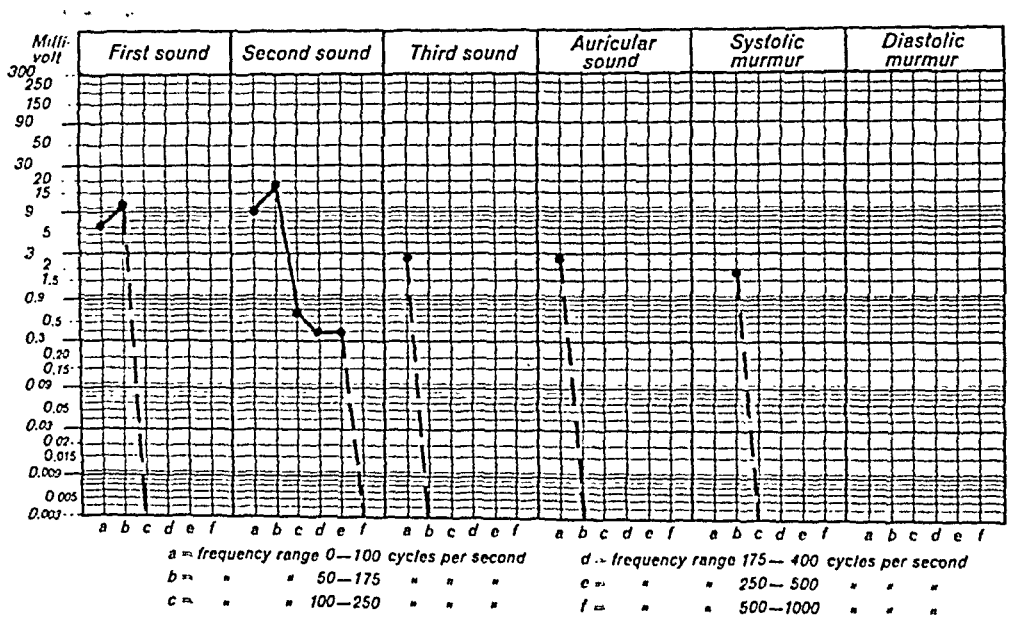




*Fig. 2. Phonocardiogram (PCG), electrocardiogram (ECG) and graphic registration of the sound phenomena of the heart in a logarithmic scale.*
Normal case, a boy of 8 years.
I = the first sound. II = the second sound. III = the third sound. IV = the auricular sound. SM = Physiologic systolic murmur.

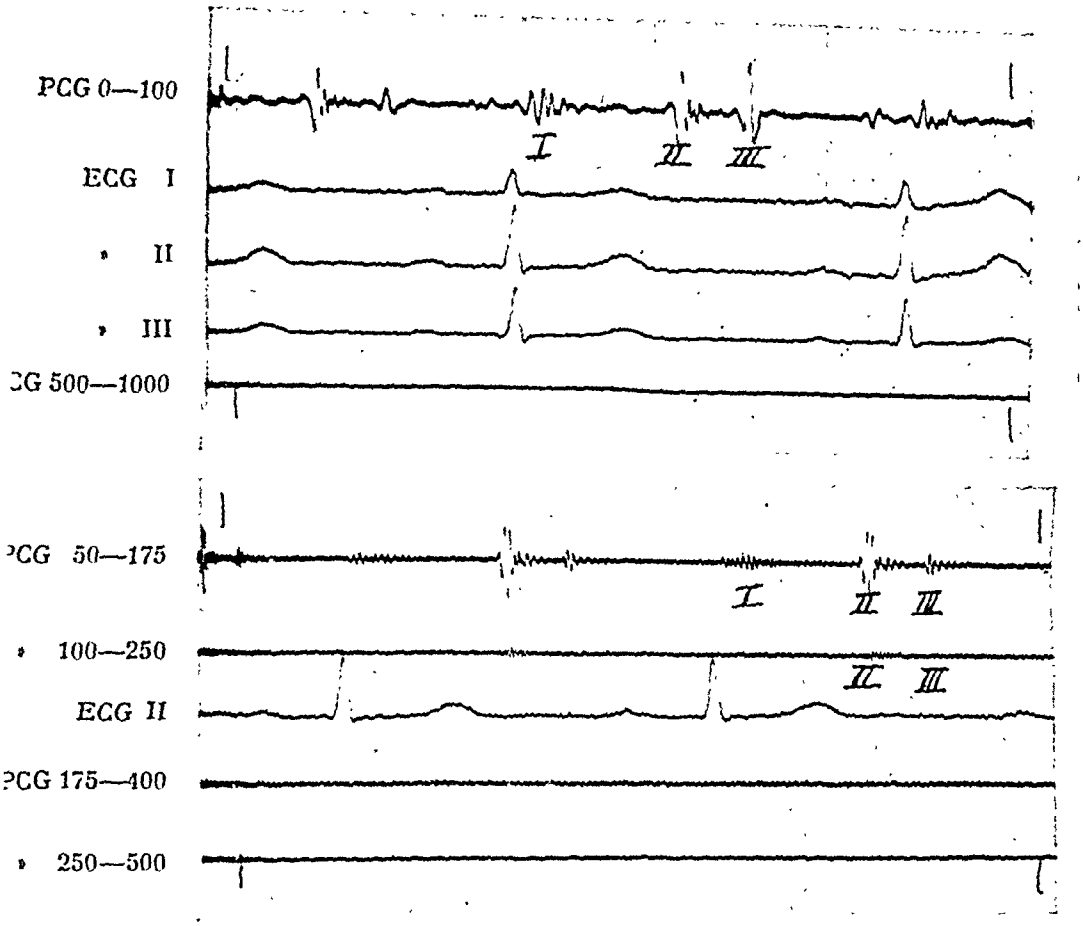



*Fig. 3. The third sound gallop. Myocarditis.*
Female, aged 22 years. (ECG 270/41) Fatigue, dyspnoea.
*The heart:* Apical systolic murmur and gallop.
*ECG:* P—Q 0.21 seconds.
*PCG:* Faint first sound with amplitude not exceeding 175 cycles per second. Systolic murmur with small amplitude 100—250 cycles per second. The third heart sound with big amplitude is registered as far as up to 250 cycles per second.

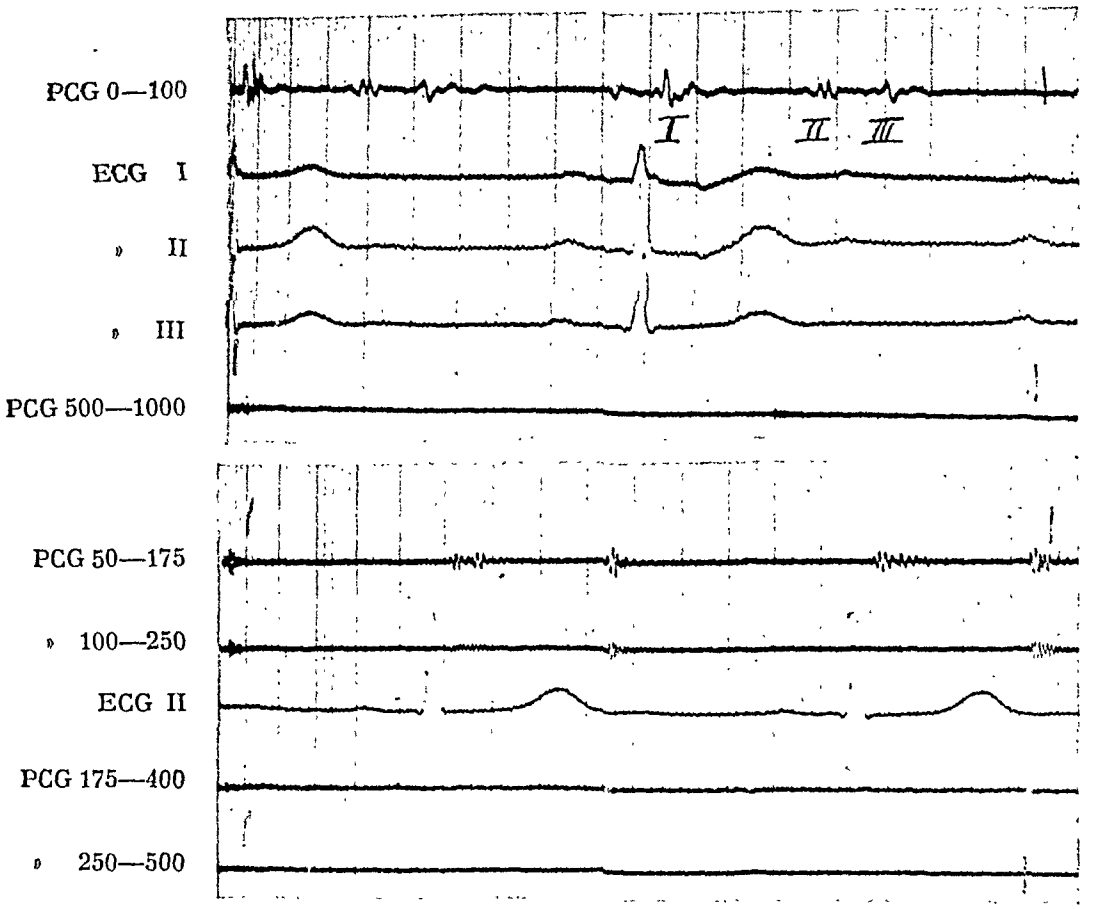



*Fig. 4. The same case as Figure 3.* Three months later. The patient is now subjectively recovered.
*ECG:* P—Q 0.17 seconds.
*PCG:* Normal third sound only registered below 100 cycles per second. The systolic murmur unchanged.

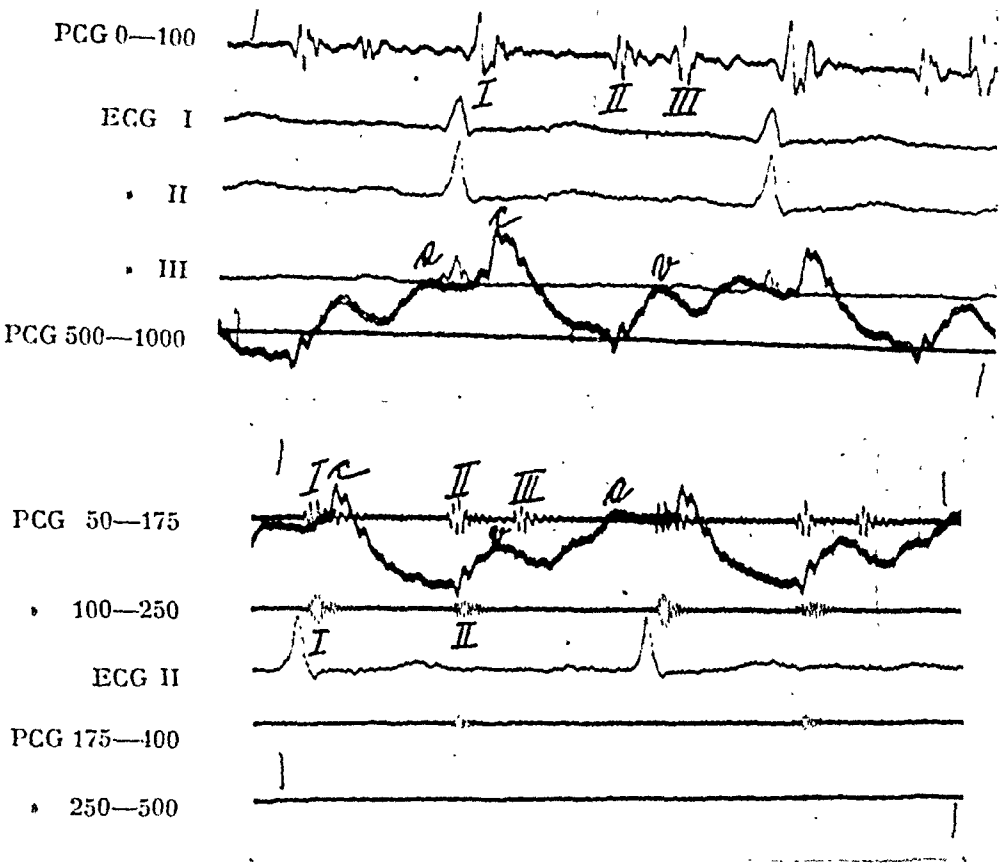



*Fig. 5. Third sound gallop. Myocardial damage.*
Female, aged 21 years. (ECG 318/41) Slight heart trouble for several years.
*The heart:* Faint systolic murmur, gallop at apex.
*X-ray of the heart:* Slight general enlargement.
*ECG:* P—Q 0.18 seconds. No definite pathologic signs.
*PCG:* Pathologic third sound registered up to 250 cycles per second.
*Venous pulse:* Third sound simultaneous with the descending line of the v wave.

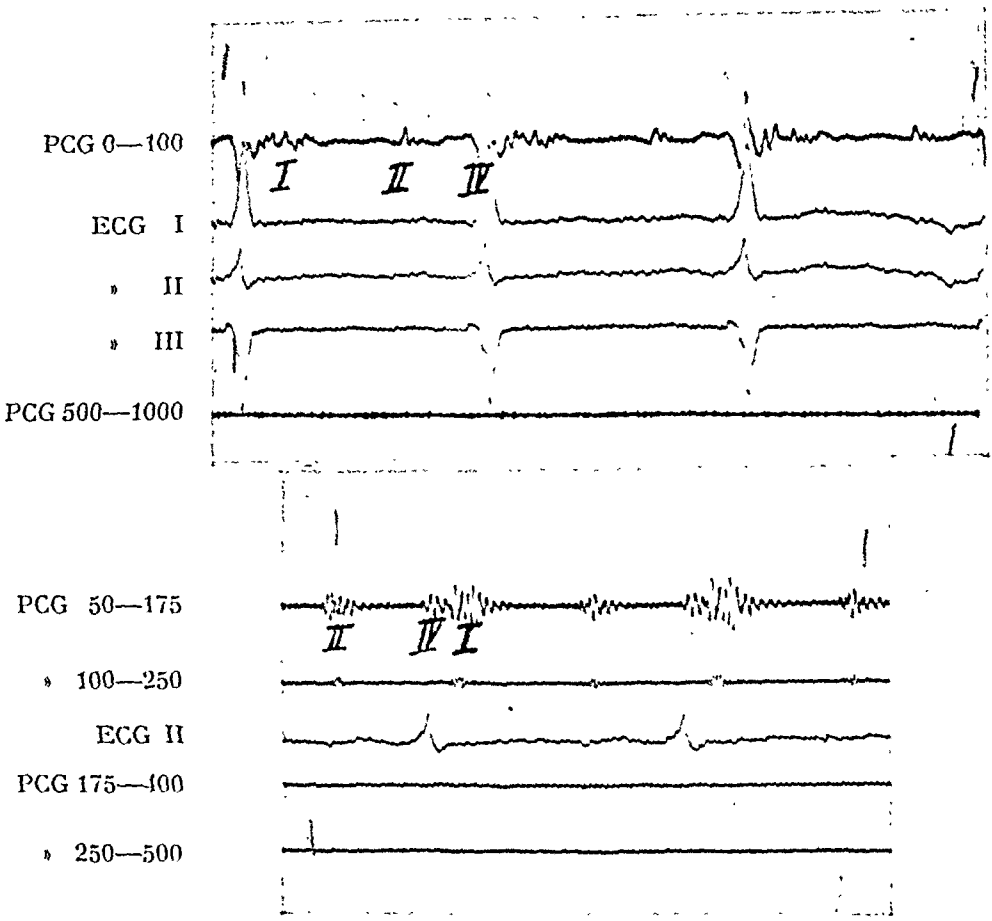



*Fig. 6. Auricular sound gallop.*
Male, aged 47 years. (ECG 874/41) Acute onset of heart failure after several months treatment for empyema of the chest.
*The heart:* Tachycardia and gallop over apex.
*ECG:* Sinus tachycardia 120 beats per minute. P—Q 0.16 seconds.
Pronounced left deviation. T I—TIII poorly developed.
*PCG:* Just before the R wave in the ECG a very loud auricular sound with over-tones reaching up to 175 cycles per second, followed by the first sound.
*X-ray of the heart:* Considerable general enlargement with posterior bulging of the auricles.

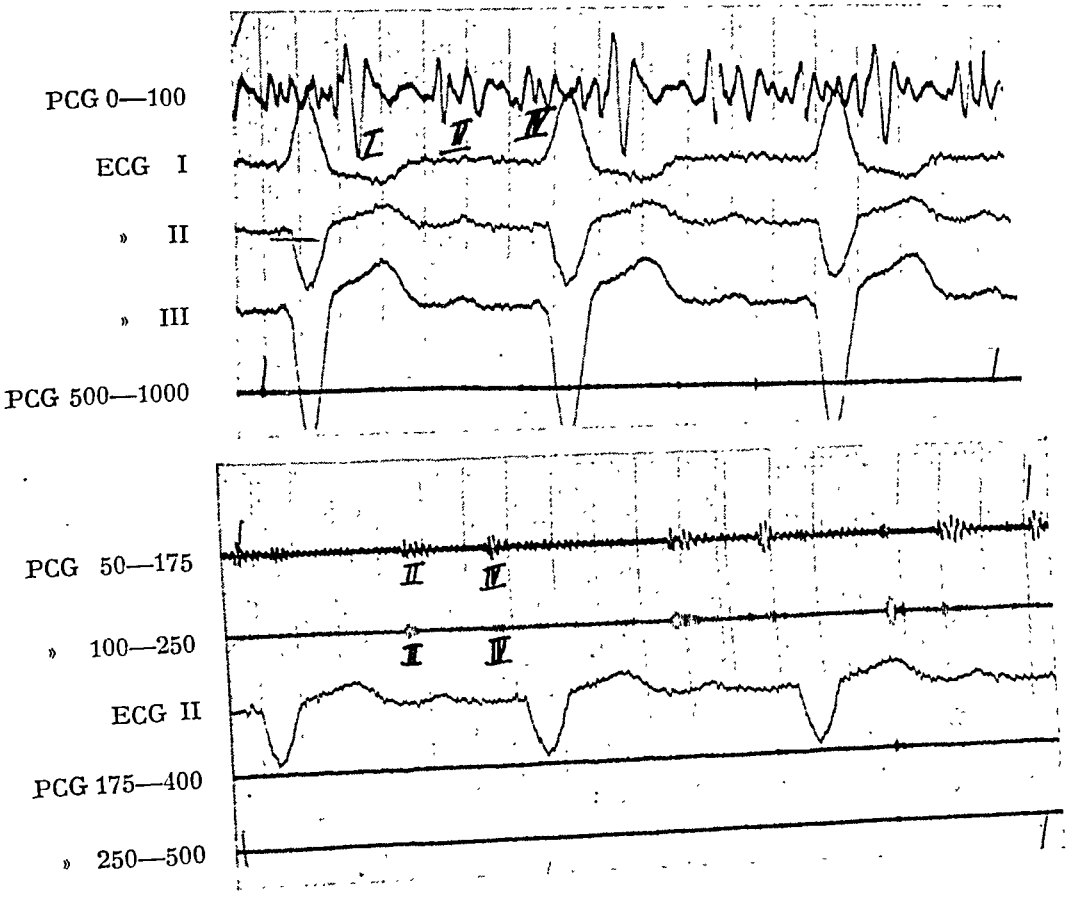



*Fig. 7. Auricular sound gallop.*
Male, aged 55 years. (ECG 917/41) Chronic myocardial insufficiency with marked dyspnoea and pronounced heart failure.
*The heart:* Muffled, rapid sounds with occasional extrasystoles. Gallop rhythm could not be auscultated.
*ECG:* Sinus tachycardia 95 beats per minute. Occasional extra systole. First grade block with conduction time 0.25 seconds. Left bundle branch block.
*PCG:* Auricular sound gallop with the auricular sound (=IV) registered up to 250 cycles per second. Duplicated second sound. Systolic murmur 50—250 cycles per second.

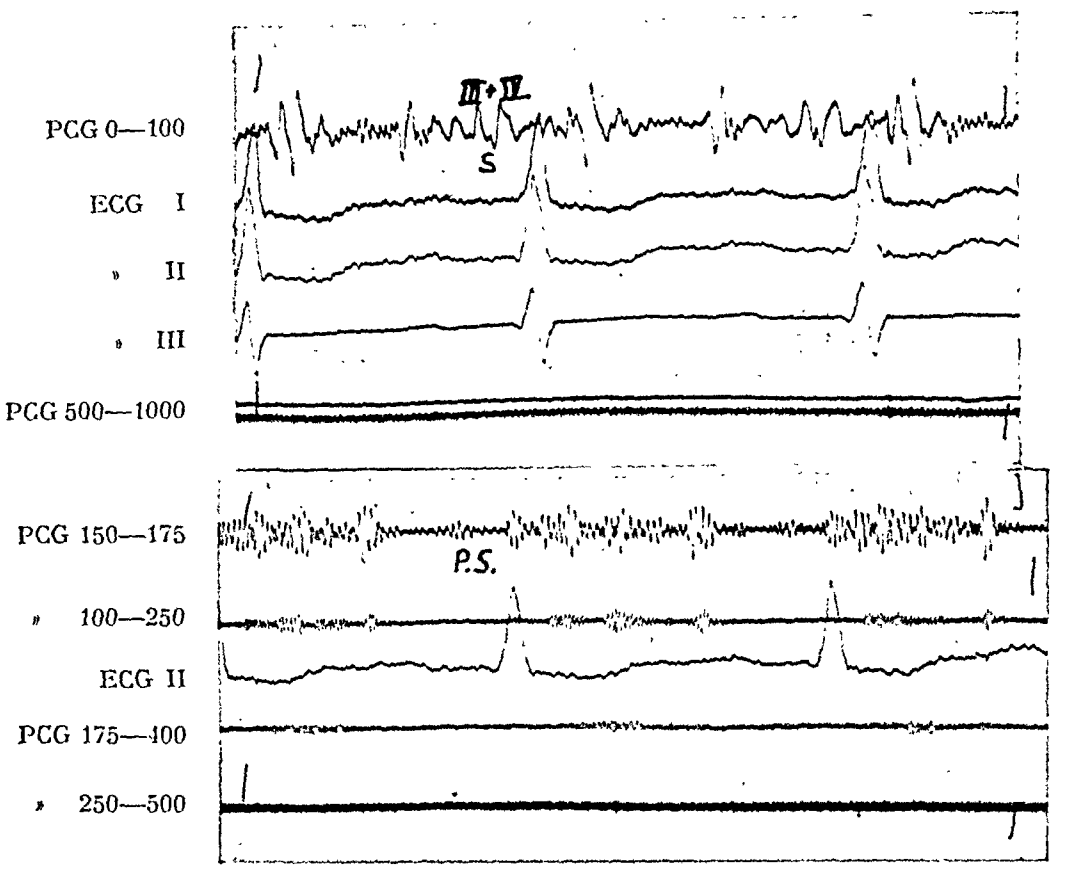



*Fig. 8. Summation sound gallop.*
Male, aged 39 years. (ECG 224/41) Mitral and aortic rheumatic valvular disease. Beginning heart failure.
*The heart:* Gallop at apex with duplicated murmur. Punctum maximum of the systolic murmur over aorta.
*ECG:* Sinus tachycardia 100 beats per minute. P—Q 0.22 seconds. Broad P waves, 0.12 seconds. T I and T II negative.
*PCG:* Summation sound gallop. The third sound (= III) and the auricular sound (= IV) have amalgamated into one sound, the summation sound (= s). Presystolic murmur 50—175 cycles per second. Systolic murmur 50—500 cycles per second.

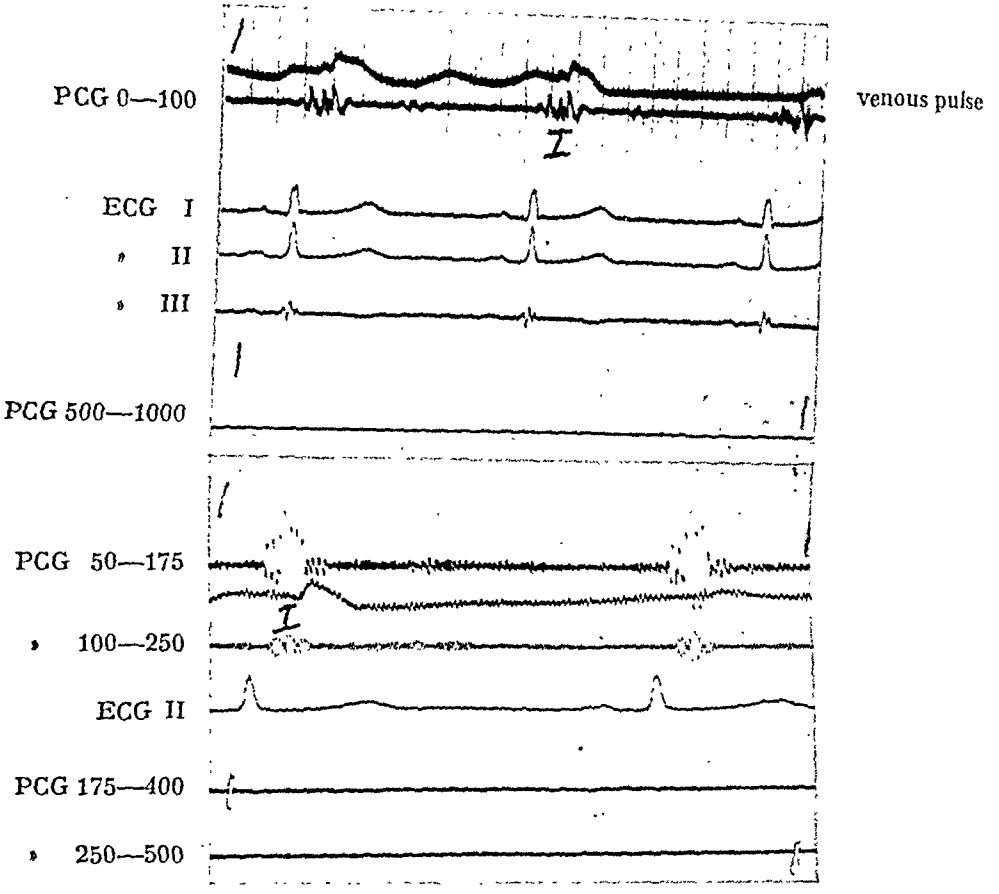



*Fig. 9. Duplicated first sound.*
Male, aged 40 years. (ECG 785/41) Treated for ulcus duodeni. No subjective heart trouble. No heart disease.
*The heart:* Gallop at apex.
*ECG:* P—Q 0.16 seconds. Pronounced Q III. Negative T III.
*PCG:* Clear duplication of the first heart sound. (= I) Not altogether free from disturbances in the high frequency ranges but no definite murmurs. Normal PCG.

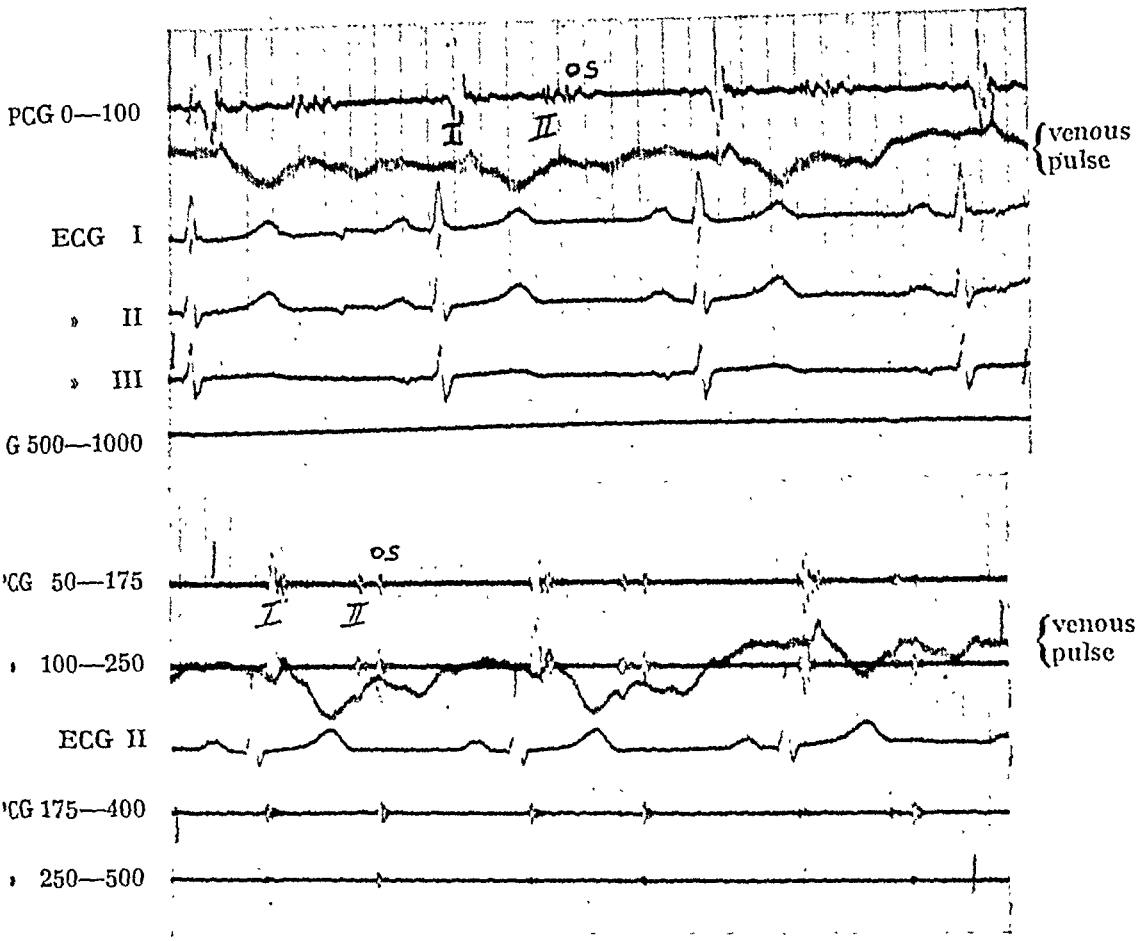



*Fig. 10. Mitral stenosis with »opening snap».*
Female, aged 39 years. Rheumatic polyarthritis and endocarditis at the age of 17 and of 27. Fairly well compensated, no edema. Pains in the heart region after exertion and excitement.
*Heart:* Accentuated first sound at apex. Rather faint systolic murmur. In the third intercostal space to the left of sternum a distinct snapping extra sound after the second sound.
*Röntgen examination of the heart (march 1942):* Bulging of left auricle both laterally and backwards. Mitral type heart.
*ECG:* Sinus rhythm 60 beats per minute. P—Q interval 0.19 sec. QRS complex normal. T wave positive in all leads. S—T intervals normal.
*PCG:* Accentuated first sound at apex. High frequency sound registered between 50—500 cycles per second, 0.08 seconds after the second sound, simultaneous with the peak of the v wave: »Opening snap of the mitral valve» (= os). Systolic murmur between 50—250 cycles per second.

## Summary.

1. The phonocardiographic registration has made the various gallop rhythms available for differential analysis in a way not possible by ordinary auscultation.

2. There are three different gallop rhythms. The first is the third sound gallop which occurs most often in ventricular dilatation. It may be looked upon as a comparatively benign sign of myocardial weakness. The second is the auricular sound gallop, a more serious symptom, appearing most commonly in mitral stenosis with enlarged left auricle. Thirdly, in rapid heart-action or prolonged conduction time a summation of the third sound and the auricular sound may occur resulting in a summation sound gallop. This gallop has the same grave significance as the auricular sound gallop.

3. The gallops have to be differentiated against duplicated first or second sounds and, also, against the opening snap of the mitral valve, a phenomenon pathognomonic of mitral stenosis (9). This sound occurs in the phonocardiogram between the second and third heart sound. The diagnosis will be facilitated by simultaneous venous pulse registration.

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# Über Albumosurie im gesunden und kranken Organismus.

Von

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(Bei der Redaktion am 11. April 1942 eingegangen.)

## Einleitung.

Obgleich die Akten über Albumoseausscheidung im Harn seit den zahlreichen darauf bezüglichen Arbeiten [1] schon geschlossen zu sein schienen, bin ich trotzdem an diese Frage noch einmal herangetreten. Die Berechtigung hiezu ergab sich aus der neuartigen und vor Allem quantitativen Bestimmungsart, die ich ausgearbeitet habe [2], aus der Anwendung der Teilung in primäre und sekundäre Albumosen auf den Harn und aus der sicheren Feststellung einer physiologischen neben einer pathologischen Albumosurie. Die Anschauungen über die Bedeutung der Albumoseausscheidung gehen sehr weit auseinander und man kann wohl sagen, dass die Albumosefrage noch immer offen ist. Krehl und Matthes [3] wollten in der Albumose die Ursache des Fiebers sehen. Dies konnte aber bald widerlegt werden, da Albumosen auch ohne Fieber gefunden werden. Es gibt kaum eine Krankheit, die nicht regelmässig oder

[1] Siehe Neubauer und Huppert, Harnanalyse, Wiesbaden 1910, wo auch die von mir nicht cit. Literatur zu finden ist.

[2] Acta Medica Skand. Bd. 109, S. 312, 1941.

[3] Deutsch. Arch. f. klin. Med. Bd. 54, 1895.

gelegentlich zu erhöhter Albumoseausscheidung im Harn Anlass geben könnte. Das gilt namentlich von den infektiösen Erkrankungen. Ein besonderes Interesse fand die Feststellung der Albumosurie beim Magenkrebs. Pacanowsky[1] meint sogar, dass sie überhaupt für das Carcinom charakteristisch sei, während sie Brieger nur beim Magen-Darmkrebs, dagegen nicht bei anderen Lokalisationen gefunden hat.

*Die Feststellung eines regelmässigen, schon physiologischen Vorkommens von Albumosen im Harn verlangt eine völlige Neuorientierung in der Albumosefrage.* Wenn auch die normale Menge nicht gross ist — ihr oberer Grenzwert liegt beim erwachsenen gesunden Mann bei 2 mg Tyrosinwert pro die — so kann doch dieser Befund dort, wo es sich um relativ niedrige Werte handelt, zu Irrtümern Anlass geben. Bei der physiologischen Albumosurie findet man aber stets nur Deuteroalbumose, während in Krankheiten zwar überwiegend auch nur Deuteroalbumose, daneben aber auch Protoalbumose gefunden wird. Diese tritt aber dann zumeist quantitativ stark hinter der Deuteroalbumose zurück. Die Protoalbumose hat jedoch dadurch eine grössere Bedeutung, *dass sie auch bei geringer Menge stets auf krankhafte Veränderungen hinweist*, was differenzialdiagnostisch besonders dann von Wert sein kann, wenn die Gesamtmenge der Albumosen nicht oder nur wenig über das Normale erhöht ist. Bei der prinzipiellen Wichtigkeit dieser Feststellungen sei es mir gestattet, die Grundzüge meines Verfahrens der Albumoseuntersuchung im Harn noch einmal zu besprechen, zumal im Verlauf der Arbeit eine wichtige Fehlerquelle der Bestimmungen, die Beimengung von Nukleoalbumin, aus geschaltet werden konnte.

100—150 cm³ von der bekannten Harn-Tagesmenge werden am Wasserbad nach Ansäuerung mit verdünnter Essigsäure (bei normalsaurem Harn 1 Tropfen pro 10 cm³) eingedampft. Der Trockenrückstand wird in etwa 15—20 cm³ Wasser aufgenommen und filtriert, zum Filtrat kommen 2 Tropfen Eisessig und die dreifache Menge konc. Alkohol. Der Niederschlag — das Alkoholsediment — wird abfiltriert (am besten nach einigen Stunden), mit etwa 15 cm³ Alkohol, dem 2 Tropfen Eisessig zugesetzt werden, gewaschen und das nicht ganz lufttrockene Filter in einem Kölbchen mit kochendem

[1] Zeitschr. f. klin. Med. Bd. 9, S. 429, 1885.

Wasser unter wiederholtem Verreiben mit einem Glasstab extrahiert und erkalten gelassen. Das Filtrat beträgt ungefähr 10—15 cm³. Anfänglich wurde dasselbe schon als die reine Albumosefraktion angesehen. Obgleich nach dem Gang der Darstellung die Anwesenheit von Eiweiss ausgeschlossen zu sein schien, so ergab sich doch im Verlaufe der Untersuchungen, dass Nukleoalbumin gar nicht selten noch in dieser Fraktion enthalten ist. Dieser Eiweisskörper löst sich trotz saurer Reaktion leicht durch die Salze des Harns, weshalb man auch im Harn selbst die charakteristische Nukleo-Albuminprobe zumeist erst nach mehrfacher Verdünnung erhält. So kann auch in dieses Extrakt Nukleoalbumin übergehen, so dass man häufig mit verdünnter Essigsäure noch eine Trübung bekommt. Diese Reaktion wurde anfänglich[1] der Protoalbumose zugeschrieben, später konnten aber durch Aussalzung mit Ammoniumsulfat und nochmalige Extraktion des Niederschlags mit kochendem Wasser bei saurer Reaktion *völlig nukleoalbuminfreie* Albumosefraktionen erhalten werden. Hat man ein Extrakt vor sich, welches keine Trübung mit verd. Essigsäure in der Kälte und nach dem Erhitzen und Wiedererkalten (Nukleoalbumin-Verstärkungsreaktion) gibt, so kann man sicher sein, die Albumosefraktion rein vor sich zu haben. Noch empfindlicher als die Essigsäureprobe ist die Sulfosalizylprobe, wobei wieder stets erhitzt und erkalten gelassen wird (Sulfosalizyl-Verstärkungsreaktion). Eine positive Sulfosalizylreaktion kann aber auch von Protoalbumose herrühren. Wir prüfen daher die Albumosefraktion, indem wir zunächst zu ca. 1 cm³ 2 Tropfen einer 20 %igen Sulfosalizyllösung hinzufügen. Ohne Rücksicht auf den Ausfall der Probe erhitzen wir bis zum Aufkochen und bringen die Probe — am besten mit einer gleich verdünnten, unbehandelten Probe — in kaltes Wasser. Fehlen einer Trübung nach dem Erkalten beweist die Abwesenheit von Nukleoalbumin und Protoalbumose und wir können dann sicher sein, eine reine Deuteroalbumose-Fraktion vor uns zu haben. Ist die Sulfosalizylprobe aber positiv, so können wir zur Sicherheit noch die Probe mit verdünnter Essigsäure anstellen. Bei völlig negativer Nukleoalbumin-Reaktion beweist die positive Sulfosalizyl-Verstärkungsreaktion die Anwesenheit von Protoalbumose. Protoalbumose-Trübungen hellen sich ferner beim Erhitzen vollständig

[1] Die diesbezügliche Angabe in Acta Med. Scand. Bd. 109, S. 312 wird hiemit richtiggestellt.

auf. Die Protoalbumose gibt auch eine Trübung, wenn man einige Tropfen Salpetersäure hinzufügt. Doch ist diese Probe weniger empfindlich, als die Sulfosalizylreaktion. Bei allen Proben warten wir einige Minuten ab und untersuchen sowohl bei auf — wie bei durchfallendem Licht, weil mitunter eine leichte Eigen-Opalescenz der Filtrate stören kann.[1]

Hat sich die Albumosefraktion als frei von Nukleoalbumin erwiesen, so können wir versuchen, die quantitative Bestimmung mittels der von mir modifizierten Millon'schen Probe vorzunehmen.[2] In der Regel stört aber ein Niederschlag hier noch diese Bestimmung. Nur selten gelingt es, durch mehrfache Verdünnung diese Störung auszuschalten und nach dem Erhitzen schon jetzt ganz klare Millon'sche Proben ohne Niederschlag zu bekommen, welche zum Vergleich mit der Standardprobe erforderlich sind.[3] *Zumeist ist daher die Ammonsulfat-Aussalzung für eine genaue quantitative Bestimmung des Tyrosinwertes nicht zu umgehen*, auch dort, wo sich die Albumosefraktion als frei von Nukleoalbumin erwiesen hat. Wir verreiben den noch vorhandenen Teil der Albumosefraktion mit etwas Ammonsulfat in der Reibschale, so dass ein kleiner Überschuss des Salzes beim Verreiben noch gespürt wird und filtrieren klar ab. Das klare Ammonsulfat-Filtrat enthält gewöhnlich keine Substanzen mit Millon'scher Reaktion. Nur wenn freies Tyrosin vorhanden ist, finden wir im Ammonsulfat-Filtrat nach 2 facher Verdünnung mit Wasser eine Millon'sche Probe. Die Intensität der Reaktion ist in diesen relativ seltenen Fällen zwar gewöhnlich nicht stark ($\frac{1}{2}$—$\frac{1}{4}$ der Standardprobe), sie ist jedoch diagnostisch wichtig zur Erkennung von schweren Leberschäden (akute gelbe Atrophie, Carcinom-Metastasen). Zumeist aber ergibt die direkte Prüfung zweifelhaften Ausfall; wir fügen daher am besten gleich zur Gesamtmenge des auf freies Tyrosin zu prüfenden Filtrats die dreifache Menge konc. Alkohols, lassen das ausfallende Ammonsulfat (am besten im Spitzglas) kurz absetzen und giessen die sich darüber abscheidende getrübte Flüssig-

[1] Stärkere Opalescenz kann durch Filtrieren mit Talkzusatz beseitigt werden.

[2] Biochem. Zeitschr. Bd. 97, S. 170, 1919, Bd. 110, S. 258, 1920, und Acta Med. Scand. l. c.

[3] Auch anscheinend geringfügige rötliche Niederschläge in der Millon'schen Probe, welche zumeist durch Spuren von Harnsäure bewirkt werden, setzen den Tyrosinwert deutlich herab. Rein gelbe Niederschläge, wie man sie im Ammonsulfat-Filtrat bei der Prüfung auf freies Tyrosin (s. später) erhält, stören weiter nicht.

keit ab. Wir waschen einmal mit Alkohol nach, vereinigen diesen Waschalkohol mit dem Hauptteil und dampfen am Wasserbad ab. Den Trockenrückstand nehmen wir in einigen cm³ Wasser auf und prüfen, am besten auch hier nach zweimaliger Verdünnung mit Wasser, auf Tyrosin.

Der Ammonsulfat-Niederschlag, der alle Albumosen und eventuell noch vorhandenes Nukleoalbumin enthält, wird mit Ammonsulfat-Wasser gewaschen, dann samt dem Filter in ein Kölbchen gebracht, mit etwa 10 cm³ aqua dest. übergossen, 1 Tropfen Eisessig hinzugefügt und unter Verreiben mit einem Glasstab einige Male aufgekocht. Wir lassen erkalten, messen die Flüssigkeit und filtrieren klar ab. *Diese Fraktion ist stets frei von Nukleoalbumin und stellt die reine Albumosefraktion vor.* In ihr können wir den Tyrosinwert in der von mir beschriebenen Weise[1] ohne Schwierigkeit bestimmen. Wir berechnen diesen Wert pro die oder die ungefähre Menge der Albumosen selbst durch Multiplikation des Tyrosinwertes mit 30. Nur in sehr seltenen Fällen, wenn noch ein störender rötlicher Niederschlag sich bei der Millon-Probe absetzt, kann es sich als notwendig erweisen, eine nochmalige Ammonsulfat-Aussalzung mit dem vorhandenen Rest vorzunehmen und in der gleichen Weise zu verfahren. Hier bekommen wir auch bei sehr kleinen Tyrosinmengen stets reine Millon-Reaktionen ohne Niederschlag.

Der Tyrosinwert der Albumosen ist, wie schon betont wurde, zumeist ein reiner Deuteroalbumosewert. In den seltenen Fällen, wo Protoalbumose nachweisbar ist, können wir aus der Sulfosalizyl-

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[1] Für die quantitative Ausführung der Millon'schen Probe benötigen wir folgende Reagenzien:

1. Hydrarg. oxydati sulf. 10.0
   Ac. sulf. conc. 10.0
   Aquae dest. 190.0
2. ½ procentige Natriumnitritlösung.

Zu 3 cm³ einer reinen 1: 50,000 Tyrosinlösung[1] kommen 2 cm³ von Lösung 1 und 3 Tropfen von Lösung 2. Es wird aufgekocht in einer Eprouvette von etwa 20 mm Tiefe und an der Luft erkalten gelassen. Diese Reaktion stellt die Standard Millon-Probe vor. Die zu untersuchenden Flüssigkeiten werden nach eventueller Verdünnung in derselben Weise untersucht und der Tyrosinwert bestimmt (2, 3fach oder ½ der obigen Standardlösung). Statt der nur wenige Stunden haltbaren Standardprobe mit reinem Tyrosin können wir zweckmässigerweise eine einmal ausgewertete, mit Chloroform konservierte Albumoselösung mit gleich starker Millon'scher Probe verwenden, welche einen Tag unverändert bleibt.

[1] Der Firma Hofman La Roche in Basel bin ich für die Überlassung von Tyrosin zu Dank verpflichtet.

Verstärkungsreaktion (selbstverständlich bei Abwesenheit von Nukleoalbumin) uns eine ungefähre Vorstellung über ihre Quantität bilden.[1] Eine 1: 50,000 entsprechende Millon'sche Reaktion ergibt, wenn sie nur oder überwiegend durch Protoalbumose bewirkt wird, eine starke, eine 1: 250,000 Tyrosin entsprechende Ver-

## I. Die physiologische Albumosurie und

Tabelle

Albumoseausschei-

| Name, Alter u. Gewicht | Geschl. | Diagnose |
|---|---|---|
| 1. R. *Jansson*, 17, 63 Klgr. | *m* | *Abgel. Hepatitis* |
| 2. R. Landén, 19, 56 » | » | » Pneumonie |
| 3. K. Strandell, 21, 60 » | w | » Hepatitis |
| 4. A. Redén, 32, 59 » | » | Dolores abdominis |
| 5. S. Augustin, 51, 70 » | m | » » |
| 6. A. Weiss, 26, 64 » | w | normal |
| 7. B. Eld, 34, 66 » | » | » |
| 8. L. Broberg, 29, 61 » | » | Post abortum |
| 9. I. Brundin, 40, 75 » | m | Lymphoma benign. |
| 10. B. Almster, 10, 26.5 » | » | normal |
| 11. R. Lars, 7 ½, 23.5 » | » | Erythema nod. (abgelaufen) |
| 12. Eigen, 63, 61 » | » | normal |
| 13. » » » » | » | Tagharn von 7 Stund. = 160 cm³ |
| 14. » » » » | » | Abendh. nach Hauptmalzeit von 6 St. = 285 cm³ |
| 15. » » » » | » | Nachtharn von 11 St. = 500 cm³ |
| 16. » » » » | » | Fleischlose Kost. Harn von 24 St. = 620 cm³ |
| 17. » » » » | » | Bries (Kalbsthymus), Harn von 24 St. = 1050 cm³ |
| 18. » » » » | » | Bries, nach Hauptmalz. u. Nachth. von 17 St. = 850 cm³ |
| 19. » » » » | » | Bries, Tagharn von 7 St. = 200 cm³ |
| 20. N. Andersson, 36, 685 » | w | Gravidität 5 Mon. |

[1] Man kann sich aus dem käuflichen Witte Pepton durch Auflösung in heissem Wasser, Filtrieren und Fällung mit konc. Salpetersäure das nötige Substrat zur Prüfung aller dieser Reaktionen leicht herstellen.

dünnung noch eine recht deutliche Trübung. Die Salpetersäure-Probe ist erst bei ungefähr der doppelten Koncentration deutlich. Es scheint ausser Proto- und Deuteroalbumose in der nukleoalbumin-freien reinen Albumosefraktion keine andere Albumose vorzukommen.

## ihre differenzialdiagnostische Bedeutung.

I.

**dung bei Normalen.**

| Besondere Reaktionen | Albumose | | Anmerkung |
|---|---|---|---|
| | Deutero-A. | Tyrosinw. | |
| — | + | 1.2 mg | Fall 6 von Tab. V, 14 Tage später |
| — | + | 1.6 » | » 4 » » III, 10 » » |
| — | + | 1.2 » | » 5 » » V, 3 Woch. » |
| Indikan | + | 0.7 » | gesund entlassen |
| — | + | 1.3 » | » » |
| — | + | 0.9 » | |
| — | + | 1.0 » | |
| — | + | 0.8 » | |
| — | + | 1.6 » | |
| — | + | 0.6 » | |
| — | + | 0.4 » | |
| — | + | 1.5 » | Normalkost, Harnstoff p. d. = 9.7 g<br>Autolyse-Koeff 1.5 : 9.7 = 0.15 |
| — | + | 0.58 » | pro Stunde = 0.083 mg |
| — | + | 0.44 » | » » = 0.073 » |
| — | + | 0.40 » | » » = 0.036 » |
| | Zus p. d. | 1.42 » | » » = 0.064 » |
| — | + | 1.25 » | » » = 0.052 » |
| — | + | 2.0 » | » » = 0.082 » |
| — | + | 1.4 » | » » = 0.082 » |
| — | + | 0·6 » | » » = 0.085 » |
| — | ++ | 5.2 » | |

Tabelle
Albumoseausscheidung

| Name, Alter u. Temp. | | | Geschl. | Diagnose |
|---|---|---|---|---|
| 1. B. Persson, | 60, | 37.9° | m | Ca? |
| 2. A. Öster, | 49, | 36.7° | » | » |
| 3. E. Lundberg, | 53, | 37.6° | w | » |
| 4. B. Gewert, | 56, | 37.5° | m | » |
| 5. A. Johansson, | 60, | 37° | » | Colitisod. Ca intest. |
| 6. A. Jansson, | 42, | 37.4° | w | Leber Ca? |
| 7. E. Erikson, | 65, | 37.2° | m | Magenblutung |
| 8. N. Kritty, | 63, | 37° | » | » |
| 9. B. Hibinette, | 71, | 37.1° | » | » |
| 10. E. Janson, | 51, | 36.6° | » | » |
| 11. G. Lönkvist, | 59, | 37.2° | » | » |
| 12. H. Rost, | 37, | 37.3° | » | Magenbeschwerden |
| 13. I. Janson, | 51, | 36.9° | » | Ca? |
| 14. O. Eklund, | 20, | 38.4° | » | Cas. inc., Tbc.? |
| 15. O. Karlsson, | 74, | 37.5° | » | Tumorverdacht |
| 16. D. Östrand, | 63, | 37.4° | » | » |
| 17. A. Fredrikson, | 56, | 40° | w | Typhusverdacht |
| 18. A. Bäverfelt, | 70, | 36.4° | » | Hepatitisod. Cholelith. |
| 19. E. Lindberg, | 75, | 38.6° | » | Unklares Fieber, Tbc.? |
| 20. A. Karlsson, | 46, | 33.9° | m | Cholelithiasis, Cholangitis? |
| 21. R. Enström, | 63, | 87.1° | » | » » |
| 22. A. Andersson, | 61, | 37.2° | » | Drüsenschwellung, Leukämie? |
| 23. R. Andersson, | 66, | 37.3° | » | Ca? |

Die physiologische Albumosurie ist ein sehr interessantes Phänomen. Albumosen wurden von verschiedenen Autoren im Blute nachgewiesen.[1] E. Wolff[2] hat bei 20 gesunden Menschen 0—60 mg Albumosen im Liter Blut gefunden. Es war daher an-

[1] Embden und Knoop, sowie Langstein, Hofm. Beitr. III., 1902. — Klewitz, Verhandl. d. deutsch. Ges. f. inn. Med. 1921, S. 466. — A. Richard, Journ. de Pharm. et de Chimie, Bd. 23, S. 111, 1921.

[2] Ann. d. Med. Bd. 10, Nr. 3, 1921.

II.
bei zweifelhaften Fällen.

| Besondere Reaktionen | Albumoe | | |
|---|---|---|---|
| | Deutero-A. | Tyrosinw. | |
| — | + | 1.2 mg | Röntgen neg. |
| — | + | 1.7 » | Chron. Gastritis |
| Urorosein | + | 2.1 » | Achylia gastr. |
| Urochromogen | + | 2.8 » | Ca ventr. |
| *Indikan* | + | 1 u. 1.2 » | Colitis |
| Bilirubin | + | 0.9 » | Cholelithiasis |
| — | + | 5 » | Ca ventr. |
| — | + | 1.2 » | Ulc. ventr. |
| — | + | 1.4 » | » » Aut.-Koeff. = 0.15 |
| — | + | 2.6 » | Ca ventr. Aut.-Koeff. = 0.30 |
| Urorosein | + | 2 u. 2.3 » | 2.3 mg bei Milchkost; Rö: Ulc. ventr., aber starre Magenwände |
| — | + | 2 « | Rö: Altes ulc. ventr., aber Befund atypisch, daher Tumorverdacht |
| — | + | 2 » | Rö: negativ. Aut.-Koeff. = 1.8 |
| — | + | 2.9 » | Tbc. pulm. |
| Indikan | + | 3.0 » | Rö: Altes ulc. penetrans ventr. |
| *Urorosein* | + | 2.5 » | Das Spital ohne sicheren Befund verlassen |
| — | + | 0.4 » | nach 3 Tagen entfiebert |
| Bilirubin | + | 0.9 » | Der weitere Verlauf spricht für Cholelithiasis |
| — | + | 0.8 » | nach einigen Tagen gesund entlassen |
| Bilirubin | +++ | 16 » | ad Operation |
| » | +++ | 14 » | » » reichlich Steine in der entzündeten Gallenblase |
| — | + | 1.3 » | Blutbefund negativ |
| — | + | 1.2 » | Aut.-Koeff. = 0.16 Röntgen neg. |

zunehmen, dass sie auch im Harn zur Ausscheidung gelangen. Ist schon das Vorkommen von Albumose im Blute Gesunder vielfach bestritten worden, so unter Anderen von Neumeister [1], so ist die Behauptung, dass im Harn normaler Menschen Albumose regelmässig vorkommt, nirgends zu finden. Eine Ausnahme bildet der Harn in der Schwangerschaft und im Wochenbett, in welchem Sta-

[1] Zeitschr. f. Biol., Bd. 24, S. 267, 1888.

delmann[1] und Fischel[2] Albumose gefunden haben. In den ausführlichen Arbeiten von Krehl und Matthes sowie von Schultess[3] wird betont, dass der Harn gesunder Menschen niemals Albumose enthält. Im Allgemeinen hat man sich damit gegnügt, die Anwesenheit der Biuret-Reaktion in den auf verschiedenste Art hergestellten Albumose-Fraktionen als Kriterium für ihre Anwesenheit zu verwenden. Wohl hat Hofmeister ein kolorimetrisches Verfahren zur Auswertung der Biuretreaktion angegeben und Maixner z. B. hat mittels dieser Methode bei Pneumonie 4 g Albumose im Tag gefunden. Aber das Verfahren hat recht wenig Anwendung gefunden, vielleicht weil es als zu wenig empfindlich angesehen wurde. Die Biuretprobe gestattet auch keine Differenzierung der Albumosen. Seit den Arbeiten der Krehl'schen Schule wurden fast durchwegs Deuteroalbumosen als Ursache dieser Reaktion betrachtet. Bei nicht fiebernden Fällen, wie Myelom, Ulcus und Ca. ventr. sollen primäre Albumosen vorkommen. Senator[4] meint, dass im Fieberharn hauptsächlich Protoalbumose gefunden wird. Aber seine Befunde sprechen eher für Deuteroalbumose. So sagt auch Hammarsten[5], dass es sich bei der Harnalbumose in der Hauptsache um Deuteroalbumose handelt.

Bei der Verfolgung der normalen Albumose-Ausscheidung ist es mir aufgefallen, dass manchmal scheinbar ohne Grund der Wert hinaufgehen kann. Ich bin diesem Verhalten in einer Reihe von Selbstversuchen nachgegangen und konnte feststellen, dass ein Teil der Albumosen exogenen Ursprungs ist und dem Nahrungseiweiss entstammt. Dabei scheint die Art des zugeführten Eiweiss die Quantität der ausgeschiedenen Albumose zu beeinflussen. Während bei einer Normalkost mit ca 120 g Fleisch die Menge der Albumosen etwa 1.5 mg p. d. betrug, stieg dieser Wert auf 2 mg, wenn statt gewöhnlichen Fleisches Bries in der gleichen Menge genommen wurde. Rein vegetabilische Kost ergab ungefähr denselben Albumosewert wie Fleischkost, so dass man annehmen muss, dass aus der nukleinreichen Thymus bedeutend mehr Albumose als Schlacke abfällt, als aus gewöhnlichem Fleisch. Es ergibt sich natürlich die Frage, ob wir berechtigt sind, die Albumosurie im Wesentlichen als

[1] Über Peptonurie, Wiesbaden 1894.
[2] Arch. f. Gyn. Bd. 24, S. 420.
[3] Deutsch. Arch. f. klin. Med., Bd. 60, 1896.
[4] Deutsch. med. Woch. 1895, Nr. 14.
[5] Lehrbuch der physiologischen Chemie, 1922.

endogen bedingt anzusehen. Dies dürfte wohl der Fall sein. Denn abgesehen von den pathologischen Verhältnissen, in welchen sich die Albumose-Ausscheidung beinahe umgekehrt proportional zur Nahrungsaufnahme, insbesonders zum Fleischgenuss verhält, ergibt die Verfolgung der Albumosewerte in Krankheiten bei möglichstem Ausschluss von Eiweiss aus der Kost keine auffallende Erniedrigung derselben. Wir sind daher wohl berechtigt, auch die physiologische Albumosurie wenigstens zum Teil als Ausdruck des normalen Gewebsabbaus zu betrachten.

Die genaue Kenntnis der normalen Albumose-Ausscheidung ist für die Beurteilung der Albumosurie in Krankheiten von grundlegender Bedeutung. Gerade das Carcinom, welches in dieser Richtung unser grösstes Interesse beansprucht, zeigt in seinen Anfängen oft keine deutlich erhöhten Werte. Die physiologische Albumosurie scheint jedoch bei beiden Geschlechtern nicht gleich zu sein. Gesunde Frauen scheiden etwas weniger aus, als gesunde Männer des gleichen Alters. Umso bemerkenswerter ist die erhöhte Ausscheidung in der Gravidität (Fall 20 Tab. I). Sie ist auch vom Körpergewicht abhängig und ist bei Jugendlichen mit geringerem Gewicht daher der absolute, aber nicht der relative Wert kleiner als bei Erwachsenen. Im Senium dürfte die Albumose-Ausscheidung erniedrigt sein. Die Feststellung der physiologischen Verhältnisse bildet die Grundlage der richtigen Beurteilung der pathologischen Albumosurie.

Da das Nahrungseiweiss sich mit einem gewissen Anteil an der Albumosurie beteiligt, so kann es sich als nützlich erweisen, die Relation der Albumose-Ausscheidung zum Harnstoffwert — als Masstab für die Eiweisszufuhr — festzustellen. Wo über die Norm erhöhte Albumose-Werte vorhanden sind, spielt diese Relation keine so grosse Rolle, da ja in diesen Fällen der endogene Anteil sicher überwiegt. Dort wo aber an der Grenze der Norm stehende Werte gefunden werden, spricht ein niedriger Harnstoffwert für verstärkten Gewebsabbau und wir bekommen vielleicht einen besseren Einblick in die Gewebs-Autolyse, wenn wir den Albumosewert pro Gramm Harnstoff feststellen. Wir besitzen in der colorimetrischen Bestimmung des Harnstoffs auf Grund der Gelbfärbung, die beim Zusatz des Ehrlich'schen Aldehyd-Reagens zu Harnstofflösungen entsteht, ein bequemes und relativ sicheres Verfahren zur Harnstoffbestimmung. Ungefähr 20 $cm^3$ Harn werden mit

einem kleinen Kaffeelöffel Knochenkohle versetzt, geschüttelt und filtriert.[1] Das vollkommen wasserfarbene Filtrat wird zuerst auf das 50-fache und dann je nach Bedarf stärker verdünnt. Von dieser Verdünnung werden 20 cm³ in eine planparalelle Flasche von etwa 40 mm Tiefe gebracht, dazu kommen 30 Tropfen oder 1.5 cm³ des Aldehydreagens. Es entsteht eine mehr oder weniger intensive Gelbfärbung. In eine ebensolche, gleich tiefe Flasche bringen wir eine reine Harnstofflösung (über Chloroform dauernd haltbar) mit einem Gehalt von 1: 10,000, geben auch hier 30 Tropfen des Aldehydreagens dazu und vergleichen die Färbungen. Ist die Farbe des verdünnten Knochenkohle-Filtrats noch stärker als die der Vergleichslösung, so verdünnen wir weiter, bis wir genau die Färbung der Standard-Harnstofflösung erhalten. Dann können wir sagen, dass die Verdünnung 1: 10,000 Harnstoff entspricht und den Wert p. d. oder in der gegebenen Harnmenge leicht berechnen. Die Heranziehung des Harnstoff-Wertes bei der Beurteilung der Albumose-Ausscheidung hat den grossen Vorteil, dass wir nicht allzu abhängig sind von der häufig unsicheren Tagesmenge des Harns und dass wir eine Relation zu einem zweiten wichtigen Harnwert bekommen, dessen Grösse auch eine gewisse Beziehung zum Albumosewert besitzt. Auf diese Weise werden auch niedrigere Albumose-Ausscheidungen verwertbarer. Die physiologische Relation Albumose: Harnstoff oder die Albumose-Ausscheidung pro Gramm Harnstoff (der Autolyse-Koeffizient) bewegt sich um 0.2 mg Albumose und erreicht selten einen höheren Wert. Bei einer einwandfreien Albumosebestimmung dürften wir berechtigt sein, höhere Autolyse-Koeffizienten schon als pathologisch anzusehen.

Betrachten wir die beiden ersten Tabellen, so ergeben sich einige wertvolle differenzial-diagnostische Gesichtspunkte. Manche klinische Schlussfolgerungen werden sich auch aus den späteren Ausführungen ableiten lassen. Jede fieberhafte Erkrankung kann zu Albumosurie Anlass geben. Doch tun dies naturgemäss vor Allem die ernsteren, mit Gewebsschädigung verbundenen Fälle. Wir können daher aus einem normalen Albumosewert bei einem zweifelhaften fieberhaften Zustand umgekehrt schliessen,

[1] Stärker gefärbte Harne verdünnt man zweckmässigerweise vor der Behandlung mit Knochenkohle einigemale mit Wasser.

dass eine stärkere Gewebsschädigung nicht vorliegt. *Denn die gesteigerte Gewebsautolyse ist eine der konstantesten und frühesten Begleiterscheinungen aller ernsthaften fieberhaften Erkrankungen.* Dies kann manchmal diagnostisch von grossem Wert sein. So wurde im Fall 17 der Tabelle II wegen des hohen Fiebers anfänglich auch an Typhus gedacht. Der niedrige Albumosewert liess aber diese Diagnose ausschliessen und einige Tage später war die Frau entfiebert. Fieber ist zwar ein häufiger, aber kein unbedingt notwendiger Begleiter einer entzündlich-infektiösen Erkrankung. Wir haben in derartigen zweifelhaften Fällen, die auch oft chirurgisches Interesse besitzen, in der erhöhten Albumose-Ausscheidung einen sichereren Indikator der Entzündung als in der nicht immer erhöhten Temperatur. So wurde im Fall 20 und 21 der Tab. II die Diagnose Cholangitis im Gefolge von Cholelithiasis aus dem bedeutend erhöhten Albumosewert gestellt. Die Operation bestätigte die Diagnose. Die Differenzial-Diagnose zwischen Cholelithiasis und Hepatitis kann durch die Albumose-Untersuchung eine wesentliche Förderung erfahren. Während die Hepatitis mit Ikterus ausnahmslos höhere Albumosewerte als normal zeigt, ist dies bei der unkomplizierten Cholelithiasis nicht der Fall und mehrfach konnte auf diesem Wege die richtige Diagnose gestellt werden. (Fall 6 und 18, Tab. II). Die vielfach diagnostisch schwer zu beurteilenden Magenblutungen, bei welchen die Blutung auch eine Röntgenuntersuchung verbietet, geben, wenn sie einem einfachen Ulcus ventr. entstammen, in der Regel zu keiner erhöhten Albumose-Ausscheidung Anlass. Ein normaler Wert, wie in Fall 8 und 9 der Tab. II, erlaubt mit grosser Wahrscheinlichkeit die Diagnose Ulcus simplex, während ein stärker erhöhter Wert, wie in Fall 7 wieder die Diagnose Ca ventr. fast mit Sicherheit stellen lässt. Leider finden wir beim Ulcus ventr. viele atypische Fälle, die nicht nur klinisch und röntgenologisch, sondern auch im Albumosebefund sich als Grenzfälle erweisen (Fall 11, 12 und 15, Tab. II). Chirurgische Affektionen, namentlich Eiterungen scheinen ausnahmslos erhöhte Albumosewerte zu liefern, und es kann auch manchmal die Therapie von dieser Tatsache Nutzen ziehen. So wurde in Fall 1 Tab. V ein Leberabscess nach Sulfapyridin-Behandlung nicht nur afebril, sondern auch in Bezug auf die Albumose-Ausscheidung ganz normal.

## II. Albumose-Ausscheidung bei Infektionskrankheiten.

Die Tabelle enthält eine Auswahl aus dem Krankenmaterial der Klinik. Die Pneumonie nimmt naturgemäss den ersten Platz ein. Wir finden bei dieser Krankheit Albumosewerte zwischen 10—30 mg, ausnahmsweise auch niedrigere Werte. In der

Tabelle
Albumoseausscheidung bei

| Name, Alter u. Temp. | | | Diagnose | Besondere Reaktionen |
|---|---|---|---|---|
| 1. H. Erikson, | 47, | 38.4° | Pneumonie | Urobilin |
| 2. G. Erikson, | 36, | 40° | » | » |
| 3. I. Boström, | 28, | 38.2° | » | » |
| Idem, 1 Tag später | | | » | » |
| 4. R. Landén, | 19, | 38.5° | » | » |
| 5. V. Brodin, | 19, | 40.3° | Broncho-Pneumonie | — |
| 6. K. Rensköld, | 15, | 37.8° | » » | — |
| 7. R. Lundquist, | 27, | 38.3° | Pneumonie u. Diabetes | Sacharum u. Azeton |
| 8. E. Björklund, | 52, | 38.5° | Lungengangrän | — |
| 9. I. Larsson, | 69, | 38.2° | Septische Erkrankung mit Tetechien | Urochromogen |
| Eadem, 3 Wochenspäter, | | 37° | » » | — |
| 10. A. Brage, | 50, | 38.8° | Akutes Fieber unbek. Ursprungs | Urochromogen |
| Eadem, 14 Tage später, | | 36.8° | » » | — |
| 11. A. Bodin, | 17, | 40° | Typhus | Urochromogen Urobilin |
| 12. G. Andersson, | 25, | 38.2° | Polyserositis: Pleuritis u. Pericarditis | |
| 13. O. Venkvist, | 40, | 38.6° | Erysipel | Urochromogen |
| 14. M. Pettersson, | 30, | 38.8° | Dermatomyositis | » |
| 15. N. Orstadius, | 31, | 39.9° | Parotitis epid. | » |
| Idem 2 Tage später, | | 37.3° | » » | — |
| » 6 » » | | 36.7° | » » | — |
| 16. H. Andersson, | 20, | 37.4° | Periarteriitis nod. | Urochromogen Urobilin |
| 17. H. Persson, | 63, | 37.8° | Pneumonie | — |
| Eadem, 5 Tage später, | | 37.4° | » | — |
| » 10 » » | | 36.5° | » | — |
| 18. K. Johansson, | 29, | 37.8° | Scarlatina | Urochromogen |
| 19. A. Andersson, | 54, | 38° | Morbilli | — |
| 20. R. Lars, | 7½, | 37° | Erythema nod. | Urochromogen |
| 21. A. Fernström, | 25, | 38.5° | Febris undulans | |

Literatur wird darauf hingewiesen, dass die Albumose-Ausscheidung erst im Stadium der Lösung beginnt. Da gegenwärtig gleich nach der Aufnahme mit der Sulfapyridin-Behandlung begonnen wird, ist eine scharfe Trennung zwischen dem Stadium der Anschoppung und dem der Lösung schwer durchführbar. Nach den Werten in Fall 3 der Tabelle — 14 mg vor und 30 mg nach Beginn

III.
**Infektionskrankheiten.**

| Albumosen | | | Anmerkung |
|---|---|---|---|
| Proto-Alb. | Deutero-A. | Tyrosinwert. | |
| 0 | +++ | 11 mg | Sulfapyridin |
| 0 | +++ | 20 » | » |
| 0 | +++ | 14 » | » begonnen |
| + | ++++ | 30 » | |
| 0 | ++ | 5 » | |
| + | ++ | 6 » | |
| 0 | ++ | 4 » | |
| + | +++ | 16 » | |
| + | +++ | 17 » | Exitus letalis |
| 0 | +++ | 16 » | Aetiologie unbekannt |
| 0 | + | 1 » | Heilung |
| 0 | +++ | 12 » | |
| 0 | + | 1.5 » | Heilung |
| + | +++ | 25 » | |
| 0 | +++ | 13 » | Tbc? |
| ++ | +++ | 12 » | |
| ++ | ++++ | 30 » | |
| 0 | ++++ | 32.4 » | |
| 0 | ++++ | 29.4 » | |
| 0 | + | 3.8 » | Entlassen |
| 0 | + | 4.5 » | |
| 0 | +++ | 12.7 » | Sulfapyridin |
| 0 | + | 2.8 » | Besserung |
| 0 | + | 1.7 » | Entlassen |
| 0 | + | 1.6 » | |
| 0 | + | 3 » | |
| 0 | + | 0.7 » | |
| 0 | + | 2.5 » | |

der Behandlung — dürfte diese Annahme begründet sein. Wir können uns vorstellen, dass beim raschen Zugrundegehen einer so grossen Zahl von Leukocyten, wie sie nach der Sulfapyridin-Behandlung einzusetzen pflegt, Albumosen in grösserer Menge entstehen. Dabei ist eine Beteiligung der Protoalbumose entweder gar nicht oder nur spurenweise vorhanden. Es handelt sich bei der Lösung der Pneumonie nicht um einen eitrigen Gewebszerfall, bei dem wir vielleicht grössere Mengen von Protoalbumose erwarten dürfen, sondern um eine Autolyse des Exudats durch reichlich freiwerdende Fermente. Wenn aber die Pneumonie mit einer anderen Krankheit kombiniert ist, oder wenn, wie dies wahrscheinlich bei den sonst leichter verlaufenden Broncho-Pneumonien der Fall ist, eine Mischinfektion vorliegt, so finden wir auch hier Protoalbumose (Fall 5 und 7).

Der relativ hohe Albumosewert beim Typhus darf vielleicht eine gewisse differenzial-diagnostische Bedeutung beanspruchen. Auch in der Literatur finden wir den Hinweis, dass Albumosen bei dieser Krankheit reichlich gefunden werden.[1] So betonen auch Krehl und Matthes ihr regelmässiges Vorkommen beim Typhus. Auch hier ist Protoalbumose nur in relativ und absolut sehr geringer Menge vorhanden. Auffallenderweise ist bei keiner Krankheit dieser Gruppe eine stärkere Protoalbumose-Beteiligung zu finden. Bei manchen scheint überhaupt keine Protoalbumose gebildet zu werden, wie wir dies in dem Fall von Scarlatina und Morbilli und beim Erythema nodosum sehen, während andere eine etwas stärkere Protoalbumose-Beimengung zeigen (Fall 13 und 14). Es müssen wohl die Bedingungen für die Entstehung der Protoalbumose neben der Deuteroalbumose verschieden sein, je nach dem Substrat und nach der Art der einwirkenden Schädlichkeit. So gehören wahrscheinlich der Diplococcus pneum. und wie wir noch sehen werden, auch der Tuberkelbazillus nicht zu den typischen Protoalbumose-Bildnern, während die Eitererreger vielleicht regelmässiger Protoalbumose abspalten dürften. Selbst ein Fall von Sepsis unbekannter Ätiologie (Fall 9) zeigte nur Deuteroalbumose. Wie stark die Gewebsautolyse bei manchen Infektionen sein kann, sehen wir an Fall 15 (Parotitis epid.). Eine im Krankheitsbild und dem Verlauf nach benigne Erkrankung hat einen Albumosewert von

[1] Leick Deutsch. med. Woch. 1896, Nr. 2.

32 mg zur Folge, der eine Zeitlang auch in fieberfreien Stadium anhält, um erst nach etwa einer Woche gegen die Norm zu abzuklingen. Die akuten Exantheme (ein Fall von Scarlatina und Morbillen) gehen mit auffallend niedrigen Werten einher, ein Zeichen, dass hier mehr toxische oder allergische, als stärkere Gewebsreaktionen vorliegen. Ebenso gab ein Fall von febris undulans trotz positiver Diazoreaktion nur zu einer geringfügigen Albumose-Erhöhung Anlass. Ein Teil der Infektionskrankheiten, wie Tuberkulose und Hepatitis werden in besonderen Kapiteln besprochen werden.

## III. Albumose-Ausscheidung bei Tuberkulose.

Die Tuberkulose gehört zu jenen Infektionskrankheiten, bei welchen die Albumose-Ausscheidung regelmässig erhöht ist. Ist ja doch Gewebszerfall, wenn auch in verschiedener Ausdehnung die charakteristische Begleiterscheinung dieser Krankheit. Die Werte sind im Besonderen bei der Lungentuberkulose umso grösser, je aktiver der Prozess ist. Daher finden wir bei hohem Fieber und stark positiver Urochromogen- und Diazoreaktion erhöhte Werte. Doch gehen Albumose-Ausscheidung und Diazoreaktion nicht parallel miteinander, was dafür spricht, dass diese Reaktionen eher toxischen als geweblichen Ursprungs sind. Protoalbumose ist zumeist nicht vorhanden. In zwei Fällen von Miliartuberkulose ohne Gehirnbeteiligung war bei einer recht hohen Deuteroalbumose-Ausscheidung keine Spur von Protoalbumose zu finden, zum Beweis, dass der Tuberkelbazillus an sich kein typischer Protoalbumose-Bildner ist. Dagegen zeigte ein Fall von Meningitis tub. (Fall 4) eine deutliche Protoalbumose-Ausscheidung. Ob die Gehirnbeteiligung hiefür die Ursache bildete oder noch andere Momente dabei mitwirkend waren, liess sich nicht mit Sicherheit entscheiden. Die Apicitis mit subfebrilen oder febrilen Temperaturen hat eine etwas über der Norm stehende Albumoseausscheidung zur Folge. Inaktive Fälle verhalten sich dagegen völlig normal (Fall 12 und 13). Eine Entscheidung, ob eine tuberkulöse Infektion schon oder noch aktiv ist, kann möglicherweise durch die Albumosebestimmung getroffen werden, doch finden wir gerade hier stark an der Grenze des Normalen liegende Werte.

Tabelle
Albumoseausscheidung

| Name, Alter u. Temp. | Diagnose | Besondere Reaktionen |
|---|---|---|
| 1. A. Lindström, 23, 39° | Tbc. pulmonum | Urochromogen |
| 2. G. Jansson, 25, 40° | » miliaris | » |
| 3. A. Hellström, 66, 39° | » » | — |
| 4. R. Engström, 13, 39.2° | Mening. tub. | Urochromogen |
| 5. H. Erikson, 48, 37.7° | Tbc. pulm. | — |
| 6. E. Pettersson, 76, 37.8° | » » | Urochromogen |
| 7. A. Fernlund, 61, 37.6° | » » mit Pleuritis | — |
| 8. S. Larsson, 37, 38.2 | Tbc. pulm. | Urochromogen |
| 9. H. Kassman, 53, 38° | » » | — |
| 10. A. Eklund, 20, 38.2° | Apicitis? | — |
| 11. E. Bäckström, 37, 37° | Peritonitis tub. | Urochromogen |
| 12. I. Larsson, 23, 37.4° | Pleuritis peracta | — |
| 13. H. Mattson, 41, 36.7° | Apicitis | — |
| 14. A. Östblom, 26, 37.8° | Tbc. pulm. | — |
| 15. G. Johansson, 30, 39.6° | » » | Urochromogen |

Tabelle
Albumoseausscheidung

| Name, Alter und Temp. | Diagnose | Besondere Reaktionen |
|---|---|---|
| 1. G. Nydal, 41, 39.6° | Leberabscesse | Bilirubin |
| Idem, 3 Woch. später, 36.8° | » | » |
| 2. L. Erikson, 61, 37.8° | Hepatitis | Bilir. u. Urob. |
| 3. G. Westerlund, 15, 36.2° | » | » » |
| 4. A. Lundell, 13, 36.1° | » | Etwas Bilir. |
| 5. B. Strandell, 21, 36.8° | » | Bilir. u. Urob. |
| 6. R. Jansson, 17, 37.1° | » | » » |
| 7. S. Österberg, 18, 38.2° | » | » » |
| 8. E. Sahlin, 35, 36.9° | » | » » |
| 9. E. Gustavsson, 18, 37° | » | Tot. Verschluss ind. 3 Woche |
| 10. A. Bergman, 65, 36.8° | Cirrhosis hepatis | Bilirubin |
| 11. O. Karlsson, 46, 38.9° | Cholelith., Cholangitis? | Tot. Verschluss |
| 12. A. Ekvall, 66, 36.6° | Ak. gelbe Leberatrophie | Bilirubin |
| 13. R. Enström, 63. 37.5° | Cholelith., Cholangitis | Bilir. u. Urob. |
| 14. E. Pettersson, 76, 38.5° | Degeneratio hep. | Bilirubin? |
| 15. O. Uppströmer, 77, 36.6° | Carcinoma, Leber-Metastasen? | Bilirubin u. Urobilin |

IV.
**bei Tuberkulose.**

| Albumosen | | | Anmerkung. |
|---|---|---|---|
| Proto-Alb. | Deutero-A. | Tyrosinw. | |
| + | +++ | 15 mg | |
| 0 | +++ | 16 » | Exitus letalis |
| 0 | +++ | 14 » | » » |
| ++ | +++ | 18 » | » » |
| 0 | ++ | 6 » | |
| + | ++++ | 30 » | » » |
| 0 | ++ | 8 » | |
| 0 | ++ | 5.5 » | |
| 0 | +++ | 18 » | |
| 0 | + | 2.6 | Pirquet stark pos. Der weitere Verlauf für Tbc. sprechend |
| 0 | ++ | 5.2 » | |
| 0 | + | 1.0 » | wahrscheinlich inaktive Fälle |
| 0 | + | 1.2° | wahrscheinlich inaktive Fälle |
| 0 | ++ | 6.4 » | Aut.-Koeff. = 6.4: 15 = 0.42 |
| 0 | ++ | 8 » | » » = 8: 7.2 = 1.1 |

V.
**bei Leberleiden.**

| Das Alkohol-Sediment | | | | Anmerkung |
|---|---|---|---|---|
| Proto-Alb. | Deutero-A. | Tyrosin-wert | Tyrosin-frei | |
| 0 | +++ | 10 mg | 0 | nach Gallenblasen Oper. |
| 0 | + | 1 » | 0 | nach Sulfapyridin-Beh. |
| 0 | +++ | 11.4 » | 0 | |
| 0 | ++ | 5.2 » | 0 | |
| 0 | + | 3.5 » | 0 | |
| 0 | +++ | 15 » | 0 | |
| 0 | ++ | 7.3 » | 0 | |
| 0 | +++ | 11.2 » | 0 | |
| 0 | ++ | 5.1 » | 0 | Autolyse-Koeffizient 0.42 |
| 0 | ++ | 6.5 » | 0 | |
| 0 | + | 1.4 » | 0 | |
| 0 | +++ | 18 » | 0 | ad Operation |
| 0 | ++ | 6 » | 2 mg | Exitus let. |
| schwach + | +++ | 14 » | 0 | ad Operation |
| 0 | +++ | 24 » | 1.5 mg | Obd.: Lungentub. mit fettiger Degeneration d. Leber |
| + | ++ | 6 » | 0.3 » | Aut.-Koeff. = 0.8 |

## IV. Albumose-Ausscheidung bei Leberleiden.

Die Leber gehört zu jenen inneren Organen, deren Stoffwechsel wohl am genauesten studiert ist. Nichtsdestoweniger vermissen wir systematische Untersuchungen über das Verhalten der Albumosen. Die Leber bietet auch darum noch ein besonderes Interesse, weil sie ausser den tyrosinhaltigen Albumosen auch freies Tyrosin bei ihrem Abbau liefern kann. Gerade das letztere fristet in der Medizin mehr ein Scheindasein, da der exakte mikroskopische Befund, auf den bisher der Nachweis gegründet war, nur selten gelingt. Es darf daher vielleicht als ein Fortschritt in der physiologisch-chemischen Diagnostik betrachtet werden, dass es auch möglich ist, in der Albumosefraktion das freie Tyrosin zu fassen und mittels der Trennung durch die Ammonsulfat-Aussalzung gesondert zu bestimmen. Die Albumose, die bei Lebererkrankungen gefunden wird, ist fast stets Deuteroalbumose. Protoalbumose scheint nur ausnahmsweise und dann in sehr geringer Menge vorzukommen.

Die häufigste Lebererkrankung, die Hepatitis oder der Ikterus kat. hat regelmässig auf der Höhe der Erkrankung eine vermehrte Albumose-Ausscheidung zur Folge. Die von mir gefundenen Werte bewegen sich zwischen 4—15 mg p. d. Leichtere Formen scheinen weniger Albumose zu liefern, als die relativ schwereren. Doch braucht trotz totalen Verschlusses der Wert nicht besonders hoch zu sein (Fall 9). Ich habe in jedem Fall von Hepatitis auch auf Tyrosin untersucht, dasselbe aber kein einziges Mal gefunden, so dass wir wohl zur Annahme berechtigt sind, dass eine schwerere Schädigung des Leberparenchyms selbst nicht vorliegt. Das relative Wohlbefinden fast aller Fälle trotz wochenlanger Gallenabsperrung spricht wohl auch in gleichem Sinne. Mitunter bietet die Differenzierung der Hepatitis von der Cholelithiasis klinisch Schwierigkeiten. Die unkomplizierte Cholelithiasis geht jedoch, wie schon erwähnt wurde, mit normalen Albumosewerten einher. Dagegen steigen diese bedeutend und über den Durchschnittswert der Hepatitis an, wenn eine Komplikation, wie Cholangitis, eintritt. Fall 11 und 13 mit den relativ hohen Werten von 18 und 14 mg Albumose p. d. beleuchten dieses Verhalten. Ein Leberabscess nach Gallensteinoperation bietet darum ein besonderes Interesse, weil es durch Sulfapyridinbehandlung innerhalb drei Wochen gelang, ihn klinisch zur Heilung zu bringen. Gleichzeitig ging der

Albumosewert von 10 auf 1 mg herunter. Die Lebercirrhose, von der mehrere Fälle untersucht wurden, zeigt auffallenderweise normale Albumosewerte und auch kein freies Tyrosin.[1] Brieger hat bei der Lebercirrhose Albumose ganz vermisst und auch Schultess hat drei Fälle mit negativem Ergebnis untersucht. Die Carcinom-Metastasen in der Leber brauchen absolut keine allzu hohen Werte zu zeigen, doch vermissen wir bei darauf gerichteter Untersuchung fast niemals freies Tyrosin. Dass die akute gelbe Leberatrophie beides — erhöhten Albumosewert und freies Tyrosin — zeigt, bedarf keiner näheren Begründung. In einem Fall von fettiger Leberdegeneration bei einer letal verlaufenden Lungentuberkulose wurde ein Albumosewert von 18 mg und daneben 1.5 mg freies Tyrosin gefunden (Fall 14). Ein besonderes differenzial-diagnostisches Interesse bieten die Erkrankungen des ductus choledochus oder des Pankreas, welche auch ohne Metastasen in der Leber einen schweren Ikterus herbeiführen können. Bezüglich dieser Fälle wird auf die Albumosurie bei Tumoren verwiesen.

## V. Albumose-Ausscheidung bei Bluterkrankungen.

Die Albumosurie bei Bluterkrankungen zeigt ein wechselndes Bild, je nachdem die Erythrocyten oder Leukocyten betroffen sind. Die unkomplizierte Anaemia perniciosa scheint nur relativ selten zu einer besonderen Erhöhung des Albumosewertes Anlass zu geben. Zumeist finden wir normale oder wenig über das Normale erhöhte Werte. Anders ist es schon bei den sekundären Anaemien aus verschiedener, zum Teil unbekannter Ursache. Im Fall 7 und 8 weist die positive Diazoreaktion auf eine toxisch-infektiöse Ätiologie hin, deren Wesen sich allerdings der näheren Erkenntnis entzog. Im Falle 10 lag eine haemolytische Anaemie nach Angina vor. Die infektiöse Genese dieses Falles dürfte auch aus der Nierenbeteiligung (½ ‰ Albumen) hervorgehen. Nicht in allen Fällen lässt sich die erhöhte Albumose-Ausscheidung begründen. So schied Fall 11, eine histaminrefraktäre Anaemie nach vor mehreren Jahren vorgenommener Magenresektion 6.5 mg Deuteroalbumose aus und zeigte einen auf das Doppelte erhöhten Autolyse-Koeffizienten. Die Leukämie (Fall 12 und 13) hat, soweit das kleine Material ein Urteil

[1] Anm. bei d. Korr.: Ein jüngst untersuchter vorgeschrittener Fall zeigte einen Wert von 5.2 mg., kein Tyrosin.

Tabelle
Albumoseausscheidung

| Name, Alter u. Temp. | | | Diagnose | Besondere Reaktionen |
|---|---|---|---|---|
| 1. E. Erikson, | 66, | 36.6° | Anämia pernic. | Urosein |
| 2. M. Åman, | 57, | 37° | » » | Urobilin |
| 3. E. Larsson, | 63, | 38° | » » | » |
| 4. B. Andersson, | 62, | 36.9° | » » | Urosein |
| 5. M. Åhlander, | 68, | 36.7° | » » | » |
| 6. H. Pettersson, | 72, | 36.5° | » » | » |
| 7. G. Karlsson, | 69, | 37.6° | » » | » |
| 8. I. Sköld, | 74, | 37.5° | » » | Urochromogen |
| 9. A. March, | 65, | 37° | Hypochr. Anämie aus unbek. Ursache | » |
| 10. G. Andersson, | 18, | 37° | Hämolyt. Anämie | Albumin ½ ‰ |
| 11. L. Larsson, | 27, | 37,3° | Histaminrefrakt. Anämie | Indikan |
| 12. K. Öfverberg, | 64, | 37.2° | Lymph. Leukämie | Urochromogen |
| 13. S. Oskarsson, | 57, | 38.3° | Leukämie, Myeloblast.? | — |
| 14. I. Oskarsson, | 18, | 37.3° | Lymphogranulomatose | Urochromogen |

Tabelle
Albumoseausscheidung bei

| Name, Alter und Temp. | | | Diagnose | Besondere Reaktionen |
|---|---|---|---|---|
| 1. I. Abramson, | 73, | 37.4° | Vitium cordis, Pleuratranssudat | — |
| 2. E. Ströman, | 61, | 37.5° | Vitium c., Oedeme, Struma | Urobilin |
| 3. G. Sundén, | 78, | 38° | Vitium c., Nierenschädigung? | Albumin |
| 4. L. Erikson, | 55, | 37.3° | Vitium c., Basedow, Nephritis | » 2 ‰ |
| 5. K. Dolk, | 70, | 37.1° | Aorten- Vitium, inkompensiert, | Urobilin |
| 6. V. Falk, | 63, | 37.3° | Aortitis luica | » |
| 7. H. Gustavsson, | 57, | 36.8° | Pyelonephritis? | Spur Albumin |
| 8. E. Söderman, | 80, | 36.8° | Ureterenhindernis durch tumor in abdomine | Albumin, Urochromogen |
| 9. A. Bärnström, | 14, | 36.6° | Nephritis chronica, Urämie | 1 ‰ Albumin |
| 10. A. Jansson, | 30, | 37.5° | » » | 4 ‰ » |
| 11. R. Andersson, | 39, | 37.2° | Nephritis chron. | Albumin |
| 12. I. Gustavsson, | 84, | 36.9° | Nephritis | » |

**VI.**
**bei Bluterkrankungen.**

| Albumosen | | | Anmerkung |
|---|---|---|---|
| Proto- Alb. | Deutero- A. | Tyrosinw. | |
| 0 | + | 1.5 mg | Achylie |
| 0 | + | 2.5 » | |
| 0 | + | 2 » | |
| 0 | + | 1.6 » | » |
| 0 | + | 1.6 » | » |
| 0 | + | 1.2 » | » |
| 0 | + | 2.9 » | Aut.-Koeff. = 0.23 |
| 0 | + | 3.5 » | |
| 0 | ++ | 8 » | |
| 0 | ++ | 6 » | nach Angina aufgetreten |
| 0 | ++ | 6.5 » | 1938 Magenresektion wegen ulcus, Aut.-Koeff. = 0.38 |
| 0 | +++ | 20 » | |
| 0 | ++ | 8.5 » | |
| 0 | ++ | 6.2 » | Aut.-Koeff. = 0.48 |

**VII.**
**Herz- und Nierenleiden.**

| Albumosen | | | Anmerkung |
|---|---|---|---|
| Proto- Alb. | Deutero-A. | Tyrosinw. | |
| 0 | + | 1.2 mg | |
| 0 | + | 1.6 » | Milchdiät |
| 0 | + | 4.5 » | |
| 0 | + | 6.3 » | Sehr blasser Harn, Urochrom-Retention |
| 0 | +++ | 12 » | bronchopneumonische Herde |
| 0 | +++ | 6.8 » | Wasserman pos. |
| 0 | + | 1.2 » | |
| + | +++ | 13 » | Hypernephrom? |
| 0 | +++ | 18 » | Urochrom-Retention, Obduktion: Schrumpfniere |
| 0 | +++ | 15 » | » » |
| 0 | ++++ | 24.8 » | Rest-Stickstoff erhöht, Urochrom-Retention |
| 0 | + | 3.6 » | |

zulässt, immer erhöhte Albumose-Ausscheidung zur Folge. Wahrscheinlich liegt dies an der Verschiedenartigkeit des zugrundegehenden Zellenmaterials: Kernlose Erythrocyten bei der Perniciosa, kernreiche Leukocyten bei der Leukämie. Wie schon aus dem Selbstversuch mit der nukleinreichen Thymus hervorging, dürften die Nukleine mehr Albumose liefern als anderes Gewebe. So finden wir auch bei der aktiven Tuberkulose, bei welcher die leukocytenreichen Tuberkel zerfallen, relativ hohe Albumosewerte. Dagegen ergab eine Lymphogranulomatose mit Urochromogenreaktion nur einen mässig erhöhten Wert.

## VI. Albumose-Ausscheidung bei Herz- und Nierenleiden.

Das vitium cordis im Stadium der Dekompensation scheint bei unkomplizierten Fällen keine erhöhte Albumose-Ausscheidung nach sich zu ziehen. Die Stauung kann wohl Ergüsse in die serösen Höhlen, braucht aber keinen vermehrten Gewebszerfall zur Folge zu haben. Anders aber dürfte es sich schon verhalten, wenn eine Beteiligung der Nieren aus einer stärkeren Eiweissausscheidung sich erschliessen lässt. Hier finden wir schon höhere Werte (Fall 3 und 4). Dass eine Komplikation wie bronchopneumonische Herde (Fall 5) oder ein Tumor (Fall 8) höhere Albumosewerte im Gefolge hat, können wir leicht einsehen. Dies war auch der einzige Fall dieser Gruppe, wo auch etwas Protoalbumose ausgeschieden wurde. Die Aorten-Vitien, welche vielfach eine luische Grundlage haben (Fall 6), zeigen vielleicht immer erhöhte Werte. Die chronische Nephritis scheint in allen Fällen höhere Albumosewerte zu liefern. Das Verhalten der Albumosen bei Nierenkranken wird in der älteren Albumose-Literatur viel diskutiert und die häufig dabei gefundene erhöhte Ausscheidung mit einem Zerfall des Nierengewebes selbst in Zusammenhang gebracht. Betrachten wir unsere drei Fälle von vorgeschrittener Nierenerkrankung (Fall 9, 10 und 11), von welchen zwei bei der Obduktion den Befund einer Schrumpfniere ergaben, gegenüber den leichteren Fällen, so dürfte diese Annahme viel für sich haben. Man könnte sich aber auch vorstellen, dass eine schwerere Nierenschädigung eine qualitative Veränderung des Eiweiss-Moleküls bewirkt, welches dann leichter Albumose abspaltet als das normale Eiweiss. Doch sind wohl die gefundenen Werte für eine solche Annahme nicht gross genug und auch der Charakter des

Harneiweiss bei Nierenkranken spricht in der Regel nicht für das Vorkommen eines qualitativ minderwertigen Eiweiss, wie etwa bei der Bence-Jones'schen Albumosurie infolge Schädigung des Knochenmarks.

## VII. Albumose-Ausscheidung bei Tumoren.

In der Literatur über Albumosurie nimmt das Carcinom einen breiten Raum ein. Man hoffte in der Albumose vielleicht ein Frühsymptom des Krebses zu finden. Diese Hoffnung hat sich jedoch nicht erfüllt und ich kann hinzufügen, dass trotz der Verarbeitung eines nicht unbedeutenden Materials an Krebsfällen der verschiedensten Lokalisation mit verbesserter quantitativer Methodik, diese auch mich zum Teil leitende Erwartung nur ein teilweises Ergebnis hatte. *Das Ca in seinen Anfängen ist keine Erkrankung, welche eine verstärkte Gewebs-Autolyse bewirken muss.* Damit soll jedoch nicht gesagt sein, dass nicht eine stärkere Albumosurie auch bei anscheinend noch nicht vorgeschrittenen Tumoren gefunden werden kann. Aber jene Gesetzmässigkeit, die bei vielen anderen, namentlich den infektiösen Erkrankungen in Bezug auf gesteigerte Albumose-Ausscheidung besteht, konnte für das Carcinom noch nicht sicher festgelegt werden. *Nur Krebsmetastasen scheinen regelmässig erhöhte Albumosewerte zu liefern*, was diagnostisch und prognostisch von Wert sein kann, da die Operabilität eines Tumors wesentlich von dieser Frage beeinflusst wird. Bei den ihrer Natur nach als gutartig zu bezeichnenden Tumoren des Gehirns (Fall 30 und 31), bei welchen nur der verhängnisvolle Sitz ausschlaggebend ist, war von vornherein ein höherer Albumosewert nicht zu erwarten. Auch der Skirrhus ventr., der sehr wenig zum Zerfall neigt, bot in dieser Richtung nichts Überraschendes. Eine gewisse Erwartung knüpfte sich anfangs an den nicht seltenen Befund von Protoalbumose beim Ca; doch handelte es sich bei den primären Tumoren fast stets nur um Spuren, die aber auch nicht regelmässig zu finden waren. Immerhin scheint die Feststellung der Protoalbumose bei Ca-Verdacht diese Diagnose zu stützen, nachdem dieser Körper bei Normalen niemals und in pathologischen Fällen auch nur relativ selten gefunden wird. Möglicherweise handelt es sich um sekundären, bakteriell bedingten Zerfall an der Tumor-Oberfläche, der in der Protoalbumose zum Ausdruck kommt. Die Erklärung des Pro-

Tabelle
Albumoseausschei-

| Name, Alter und Temp. | Diagnose | Besondere Reaktionen |
|---|---|---|
| 1. K. Johansson, 81, 36.9° | Carc. ventr. | — |
| 2. A. Hagström, 63, 37° | » » | Urochromogen |
| 3. R. Karlsson, 65, 36.5° | » » | Urorosein |
| 4. S. Erikson, 54, 37.6° | » » Metastasen | Urochromogen |
| 5. H. Turen, 58, 36.8° | Ca ventr., operiert Metastasen | Urorosein |
| 6. M. Larsson, 81, 36.7° | Skirrh. ventr. | — |
| 7. K. Erikson, 81, 36.7° | » » mit Leber-Metastasen | Bilirubin |
| 8. B. Berg, 80, 36.5° | Ca ventr. | Urorosein |
| 9. N. Blomberg, 73, 37.4° | » » | Urochromogen |
| 10. I. Erikson, 76, 37.2° | » » | Urobilin |
| 11. A. Andersson, 79, 37° | » » | Urob. und Urochromogen |
| 12. V. Erikson, 75, 37.8° | » » | Urorosein |
| 13. A. Löf, 73, 37.5° | » » | » |
| 14. G. Johansson, 75, 37.3° | » » | — |
| 15. E. Erikson, 73, 37.0° | » » | Urobilin |
| 16. A. Ahrburg, 61, 37.6° | » ? | — |
| 17. G. Forsberg, 66, 37° | » » | Urorosein |
| 18. H. Johanson, 75, 37.3° | » » | Urochromogen |
| 19. Ch. Westerholm, 64, 36.5° | Ca oesophagi | Indikan |
| 20. A. Vendin, 68, 37.2° | » » | Urobilin u. Urorosein |
| 21. A. Hedström, 69, 36.6° | Ca coli | — |
| 22. A. Strömberg, 65, 37.2° | Hypernephroma? | Urochromogen |
| 23. O. Ekvall, 78, 37° | Ca prostatae | — |
| 24. E. Karlsson, 83, 37.6° | » » mit Metastasen | — |
| 25. O. Uppströmer, 79, 37.5° | Ca hepatis | Urob. u. Bilir. |
| 26. K. Westergren, 63, 36.8° | Ca ventr. mit Leber-Metastasen | Urobilin |
| 27. H. Thun, 50, 38.7° | Carc. Metastasen in der Leber | Bilirubin |
| 28. H. Norlin, 60, 37.4° | Ca pankreatis | » |
| 29. E. Svensson, 70, 37.3° | » » | » |

VIII.

dung bei Tumoren.

| Das Alkohol-Sediment | | | | Anmerkung. |
|---|---|---|---|---|
| Proto-Alb. | Deutero-A. | Tyrosinw. | freies Tyr. | |
| 0 | + | 2.5 mg | 0 | |
| + | + | 3 » | 0 | |
| + | + | 2.8 » | 0 | |
| 0 | ++ | 7 » | 0 | unsicher, ob von Magen ausgehend |
| +++ | ++++ | 45 » | 0 | |
| + | + | 1.5 » | 0 | |
| + | ++ | 5 » | 0.6 mg | |
| + | ++ | 6.2 » | 0 | |
| + | + | 2.5 » | 0 | |
| 0 | + | 3.5 » | 0 | |
| 0 | + | 2.7 » | 0 | |
| + | + | 4 » | 0 | |
| 0 | + | 3.5 » | 0 | Fast der ganze Magen durch tumor ersetzt |
| 0 | ++ | 8 » | 0 | Autolyse-Koeff. = 1.2 |
| + | + | 3.2. » | 0 | Kurz danach Exit. let. |
| 0 | + | 2.2 » | 0 | Aut.-Koeff. = 0.24 |
| + | ++ | 4.8 » | 0 | » » = 0.32 röntg. bestätigt |
| 0 | + | 2.3 » | 0 | Aut.-Koeff. = 0.33 |
| 0 | + | 1.6 » | 0 | |
| 0 | + | 3.1 » | 0 | » » = 0.5 |
| 0 | + | 2.2 » | 0 | Radikal-Operation |
| 0 | + | 1.8 » | 0 | |
| 0 | + | 1.5 » | 0 | |
| ++ | +++ | 22 » | 0 | |
| + | ++ | 6 » | 0.3 » | Aut.-Koeff. = 0.8 |
| + | ++ | 5 » | 0.8 » | |
| 0 | ++ | 5.9 » | 0.5 » | Vor 2 J. Ca mammae operiert |
| 0 | + | 4 » | 0 | Operation, keine Leber-Met. |
| 0 | ++ | 9.4 » | 0 | » » » |

| Name Alter und Temp. | | | Diagnose | Besondere Reaktionen |
|---|---|---|---|---|
| 30. A. Hold, | 41, | 36.8° | Tumor cerebri | — |
| 31. M. Iansson, | 45 | 37° | Glioma | — |
| 32. I. Granath, | 72, | 37.2° | Psoas Sarkom | Urochromogen |
| 33. O. Johanson, | 27, | 37.1° | Sark. ossium? | — |
| 34. E. Gustavson, | 57, | 36.7° | Ca ventr. mit Metast. in Leber u. am Periton. | Bilirubin u. Albumin |
| 35. A. Jansson, | 61, | 36.5° | Myeloma? | Albumin |
| 36. A. Höglund, | 77, | 36.5° | Ca pankreatis? | Bilin., Oxysäuren = 75 mg p. d. |
| 37. R. Sjöblom, | 71, | 37.5° | " " | Bilir., Oxys. = 45 mg p. d. |

toalbumose-Befundes als sekundär bewirkt, lässt im Stiche bei den Ca-Metastasen mit einem bedeutend erhöhten Albumosewert, in welchem auch Protoalbumose reichlich vertreten ist (Fall 5, 24 und 34). Denn gerade die zumeist in inneren Organen sitzenden Metastasen geben ja kaum zu einem so starken bakteriell verursachten Gewebszerfall Anlass, wie er nach der Grösse des Protoalbumose-Wertes in manchen Fällen angenommen werden muss. Wir müssen daher die Frage noch offen lassen, inwieweit die bei einer grösseren Zahl von Carcinom-Fällen gefundene Protoalbumose nicht doch mit dem malignen Gewebe selbst zusammenhängt. Um die autolytischen Vorgänge beim Ca (und anderen Erkrankungen) besser erfassen zu können, wurde versucht die Relation zwischen dem Albumose- und dem Harnstoffwert ziffernmässig auszudrücken und der neue Begriff des Autolyse-Koeffizienten eingeführt (s. Fall 16 Tab. VIII und Fall 23 Tab. II). Tumoren anderer Art, wie Sarkom, hatte ich nur in geringer Zahl zu untersuchen Gelegenheit. Möglicherweise gibt die Eigenart des Sarkoms leichter zu erhöhtem Gewebszerfall und vermehrter Albumose-Ausscheidung Anlass (Fall 32).

In der Tumor-Tabelle finden wir ausser den Albumosewerten

| Das Alkohol-Sediment | | | | Anmerkung |
|---|---|---|---|---|
| Proto-Alb- | Deutero-A. | Tyrosinw. | freies Tyr. | |
| 0 | + | 1·9 mg | 0 | Erblindung |
| 0 | + | 1.5 » | 0 | Exitus let. |
| 0 | +++ | 11.2 » | 0 | Aut.-Koeff. = 1, Exit. let. |
| 0 | + | 2.8 « | 0 | |
| ++ | +++ | 24 » | 2 mg | Exit. let. Protoalb. Wert 7 mg Tyrosin entprechend. Alb. Reaktion vielleicht durch Pro toalb. bewirkt |
| 1 | | | | |
| ++ | +++ | 13 » | 0 | Protoalb. 2.5 mg Tyrosin entsprechend, Prot. = Bence Jones Eiweisskörper? |
| 0 | ++ | 7.3 » | 0 | Norm. Oxysäuren-Wert etwa 10 mg p. d. |
| 0 | +++ | 14.6 » | 0 | Aut.-Koeff. — 1.7 |

noch einige besondere Reaktionen angeführt, auf welche mit einigen Worten näher eingegangen werden soll, da sie oft wertvolle diagnostische Hinweise bieten können. Dass Bilirubin auf das Pankreas, den Duct. chol. oder die Leber selbst hinweist, braucht nicht besonders hervorgehoben zu werden. Differenzial-diagnostisch soll nochmals betont werden, dass normale Albumosewerte bei Ikterus eher für unkomplizierte Cholelithiasis als für Ca sprechen. Erhöhte Werte können sowohl bei Hepatitis wie bei Ca vorkommen. Eine nicht unwichtige Hilfe kann der Nachweis von freiem Tyrosin bilden, welches bei einfacher Hepatitis nicht gefunden wird. Differenzial-diagnostische Schwierigkeiten bieten nicht selten jene Ikterus-Fälle,welche bei Verschluss der grossen Gallenwege oder bei Pankreas-Tumoren durch Druck auf diese entstehen. Urobilinogen wird meistens vermisst und Diazoreaktion ist recht selten. Die Albumosewerte brauchen nicht auffallend hoch zu sein, so dass der pathochemische Befund sich häufig nicht wesentlich von dem einer Hepatitis unterscheidet. Ich hatte in der letzten Zeit Gelegenheit mehrere solche Fälle zu untersuchen. Der einzige auffälligere Unterschied im Harnbefund *war die relativ hohe Oxysäuren-Ausscheidung,* welche bei der Hepatitis normal ist. Dieser Befund,

der mir schon früher in ähnlichen Fällen aufgefallen war, konnte nicht immer mit der nötigen Sicherheit wegen medikamentöser Störungen durch die Salizyl-Präparate festgelegt werden, welche auch in Aether übergehen und eine Millon Reaktion bewirken können. Ein abschliessendes Urteil über die Bedeutung der Oxysäuren für die Tumordiagnose in zweifelhaften Fällen wird sich erst aus der Untersuchung einer grösseren Zahl solcher Fälle gewinnen lassen und soll daher vorläufig nur mit Vorbehalt auf diesen Befund verwiesen werden.

Das in der Tumortabelle wie auch bei anderen Fällen (s. besonders Blutkrankheiten) angeführte Urorosein und Indikan entsteht aus der Indolyl-Essigsäure und Indoxyl-Schwefelsäure und sind diese Körper Magen-Darmsymptome. Sie weisen unter Anderem oft schon sehr früh auf Achylie des Magens hin, weshalb wir ihnen (besonders dem Urorosein) auch bei der An. pern. mehrfach begegnet sind. Urobilinurie können wir manchmal beim Ca des Oesophagus und des Magens antreffen, während sie beim Leberkrebs in der Regel nicht sehr stark zu sein pflegt. Die Genese der Urobilinurie beim Magencarcinom ist eine andere als bei der grossen Mehrzahl der meisten anderen Krankheiten, wo sie auf das Herz, die Lunge oder die Leber hinweist. Sie entsteht durch Übertritt des Gallenblasen-Inhalts durch den vielfach offenen Pylorus in den Magen, wo das Urobilin rasch resorbiert wird[1]. Dazu kann sich noch eine beim Ca nicht seltene hämolytische Komponente gesellen, wodurch das Angebot an Urobilinogen im Darm und sein Gehalt in der Galle bedeutend ansteigt. Die Unterscheidung dieser gastrischen, respektive hämolytischen von der Stauungs-Urobilinurie gelingt unschwer in jenen Fällen, wo das Korrelat des Stauungs-Urobilins, das Uroerythrin, nicht oder nicht wesentlich vermehrt ist. Auf dieses Verhalten soll in einer späteren Arbeit näher eingegangen werden. Urochromogen wird beim Krebs nicht selten angetroffen. Allerdings darf man sich nicht mit der Prüfung auf Diazoreaktion begnügen, die erst in späteren Stadien stärker ausgesprochen zu sein pflegt, sondern man muss diese Reaktion durch die weit empfindlichere Permanganatprobe ersetzen und soll sie in unsicheren Fällen auch mit dem Ammonsulfat-Filtrat vor-

[1] Siehe Meinel, Centralbl. f. inn. Med. 1903 und Ladage, Inaug. Diss. Leyden, 1904.

nehmen.[1] Auffallenderweise geben viele auch anscheinend noch initiale Fälle schon eine deutliche Urochromogenreaktion, welche ohne Rücksicht auf die Ausdehnung des Tumors vorhanden sein und bei den in der Regel fieberfreien, älteren Kranken mitunter einen wertvollen diagnostischen Hinweis bilden kann.

## Zusammenfassung.

1) Es gibt neben einer pathologischen auch eine physiologische Albumosurie, welche aber niemals über einen oberen Grenzwert von 2 mg pro die hinausgeht.

2) Normalerweise wird stets nur Deutero- und keine Protoalbumose im Harn ausgeschieden.

3) In Krankheiten kann neben Deutero- auch Protoalbumose gefunden werden, doch überwiegt auch hier in den meisten Fällen die Deuteroalbumose. Erhöhte Albumosewerte kommen bei vielen Krankheiten regelmässig vor und können als Ausdruck einer vermehrten Gewebs-Autolyse angesehen werden. Die Relation zwischen der ausgeschiedenen Albumose und dem Harnstoff oder die pro Gramm Harnstoff ausgeschiedene Albumosemenge — der Autolyse-Koeffizient — überschreitet normalerweise nicht den Wert von 0.2 mg.

4) Beim Carcinom ist eine deutliche Tendenz zu erhöhler Albumoseausscheidung festzustellen, wenn auch vielleicht manche derbe Tumoren normale Werte zeigen können.

5) Auf einer in regelmässigen Intervallen vorgenommenen Prüfung der Albumoseausscheidung kann vielleicht eine rationelle Krebsprophylaxe aufgebaut werden.

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[1] Näheres s. M. Weiss, Diagnose und Prognose aus dem Harn, Verlag für Medizin, Hans Huber, Bern.

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# The abnormal electrocardiogram.

## I. Saddle-formed ST Segments.

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## Introduction.

The significance of the electrocardiogram to the diagnosis of the heart lesions is recognized generally. But if we consider critically each of the changes in the electrocardiogram that in the course of time have been pointed out by various investigators as abnormal and indicative of cardiac disease, we will soon discover that the diagnostic significance of a good many of these changes is still uncertain. Of electrocardiographic changes of unquestionable diagnostic significance, mention has to be made of the progressive changes in the ST segments and T waves appearing in myocardial infarction and pericarditis, complete auriculoventricular block and certain forms of arrhythmia, especially auricular fibrillation and auricular flutter. Most investigators also reckon negative T waves in Leads I and II as belonging to this group; and, according to our experiences, this is justified if the change in the T wave is stationary, whereas the question about the significance of transitory changes in the T waves is in need of revision.

The diagnostic significance of all the electrocardiographic changes other than the ones just mentioned seems yet rather uncertain

— for various reasons. Some electrocardiographic changes are so rare that it has not been practicable yet to collect so many cases that it would be safe to take a conclusive stand as to their significance. This applies, for instance, to electrocardiograms in which the main wave in the QRS complex in all three derivations from the extremities is negative (Burstein & Ellenbogen). Other changes have been reported so recently that only the authors who describe them have yet been able to consider their significance. This implies, for instance, to the change in the QRS complexes (preponderance of the left side with $R_{II} > R_I$) reported by Sodeman & Engelhardt. Some electrocardiographic changes reported earlier appear not to have attracted so much attention that their significance has been investigated to any great extent — for instance, the changes observed by Proger & Minnich in the QRS complexes (left preponderance with $T_I > {}^1/_7\ R_I$ and/or $S_{II} > \frac{1}{2}\ R_{II}$ and/or $T_{III} > T_I$). For a few of the reported changes, we think, the given criteria are not sufficiently distinct and detailed — as, for instance, the »second positive wave of $QRS_{III}$» reported by Katz & Slater. Further there are a number of changes which, for reasons that will not be entered into here, are still disputed as to their diagnostic significance, notwithstanding several investigations. This applies, for instance to the high waves in the QRS complexes, »low voltage», left preponderance, notching of the QRS complex, saddle-formed ST segments, and others.

In order to enable us, if possible, to make a contribution to the question about the diagnostic significance of the electrocardiogram, Professor Erik Warburg, M. D., has kindly placed at our disposal the large material collected in the Medical Department B of the Rigshospital in the course of years. Since January 1936, on the initiative of Professor Warburg, all the patients admitted to Dep. B have been electrocardiographed immediately after their admission, and in all the patients with abnormal electrocardiograph changes, the examination has been repeated frequently — in many cases, daily, or every other day through a considerable length of time. In order to be able to cope with this work, as far as the more common changes are concerned we decided to work up only the material from 1938, 1939 and 1940. In this period about 2600 patients were admitted to Dep. B, and from these patients approximately 15500 electrocardiograms were taken. The number of electrocardiograms

from each patient varies between 1 and 94. As this material will form the foundation for a series of studies, in order to avoid repetition, we shall here give an account of its composition and of the principals we have followed in working it up.

As is well known, the Rigshospital is a state hospital, receiving patients from the entire Denmark. For the medical departments the main task is to serve as a medical clinic for those parts of the country for which there is not yet any local medical department, besides from all parts of the country to receive the patients whose diagnosis and treatment give particular difficulty. Numerically, however, the latter category of patients plays no great role even though the conspicuous aspects of these cases stamp the clinics to some extent. For teaching purposes, in recent years Professor Warburg has taken care that many patients with acute medical diseases have been admitted from Copenhagen and the surrounding country. For this reason, the patient material of the department is now more like the patient material in the medical departments of the municipal hospitals than was the case previously. Still, the particular interests of this department have brought about that the number of patients with heart lesions and endocrine affections is relatively large, but of course, this is only of advantage to our purpose. Only one group of patients is lacking entirely: patients with acute epidemic diseases.

The examination of the patients may be characterized as quite thorough. Of particular examinations mention is to be made of roentgenography of the heart and lungs, which has been performed in about two-thirds of these cases — covering fully the number of patients with heart lesions, established and potential. The blood pressure is measured on all the patients, and repeatedly on the patients who showed a high blood pressure on admission. Further, the venous pressure and vital capacity have been determined often and phonocardiography is performed in many cases. The electrocardiogram is taken with a thoroughly tested amplifying apparatus from »Universitetets Instrument-Verkstad», Lund, Sweden — always in five derivations, namely: besides the derivations from the extremities, the precordial derivations *d* and *s* given by Groedel (*d:* lower left corner of the sternum — right arm; *s:* 4 cm to the left of the apex of the heart and at this level — right arm). The sites of derivation on the chest are marked off by the resident physicians of the department. In a good many cases working tests have been made with electrocardiography before and after the work, and experiments with anoxemia have been performed in a few cases.

In working up the material we have adopted this procedure: On going through the material we have noted down on special index cards all the deviations of the respective electrocardiograms from the normal values given by Kaj Larsen and Skúlason. Then we have gone through the material a second time and noted down on the other side of the index cards the summary of the history of the respective patient and the objective findings which we considered of importance to the clinical judgment of the case.

On the basis of the case histories and objective findings, without considering the abnormal changes in the electrocardiogram (with the exception mentioned in the following), we have then divided the patients into three main groups: patients with heart lesions, patients with potential heart lesions, and patients without any circulatory affection.

Our criteria for cardiac disease have been: 1) abnormal changes in the heart demonstrated on autopsy; 2) abnormal changes in the roentgenogram (the heart is designated as enlarged when its transverse diameter was greater than one-half of the transverse diameter of the chest); 3) presence of significant auscultatory anomalies, i. e., diastolic murmurs, systolic murmurs accompanied by a thrill, and pericardial friction sounds; 4) presence of definite symptoms of cardiac insufficiency — *e. g.*, marked cyanosis, oedema, hydrothorax, ascites; 5) patients with complete auriculoventricular block or with auricular fibrillation or flutter are at once entered in this group; 6) a few patients with a positive history of coronary thrombosis, but without objective signs of cardiac disease or merely with electrocardiographic changes.

Potential cardiac disease covers the following patients if they did not present any objective signs of heart lesion: 1) patients with a past or present history of rheumatic fever or repeated attacks of chorea; 2) patients infected with syphilis at least 10 years ago; 3) patients with exophthalmic goiter, myxoedema, and Addison's disease; 4) patients with hypertension, *i. e.*, a blood pressure of 150/100 or more persisting beyond one week's rest in bed; 5) patients with aortic lesions; 6) patients with severe and protracted anemia, *i. e.*, hemoglobin percentage below 50 for at least 3 months; 7) patients with diseases affecting the pulmonary circulation through a considerable length of time and giving functional dyspnea and possibly lowered vital capacity (*e. g.*, severe kyphoscoliosis, emphysema of the lungs, bronchial asthma, large cysts of the lungs, pneumoconiosis).

All the other patients are considered normal with regard to the circulation.

In the following we shall look into the significance of saddle-formed ST segments. We have selected this anomaly as the first one in the series of our studies because the saddle form of the ST segments is so frequent a change that we have been able to take our stand in the question of its diagnostic significance on the basis of the material from 1 year alone.

### *Saddle-formed ST Segments.*

The designation saddle-formed ST segment for the electrocardiographic change that will be mentioned in the following was employed first by v. Nieuwenhuizen, Hartog & Mattijssen. But this change was first assigned a diagnostic significance by Borgard in 1933. Radnai calls the same change »Koronar-R».

In this anomaly the ST segment has the form of the longitudinal section through a saddle — for instance, a longitudinal section through the sella turcica. According to Borgard's description the S wave is lacking; the descending limb of the R wave is arcuate as it enters over into the ST segment which continues as a smooth curve into the ascending limb of the T wave which is always positive. Thus the ST segment forms a downward convex curve.

Borgard's description is found in a small paper entitled »Zur Erkennung der Coronarsclerose». As to the diagnostic significance of this anomaly, Borgard says: »While the occurrence of this change in a single derivation cannot be decided as definitely pathognomonic, its simultaneous appearance it Leads I and II allows of the diagnosis coronary sclerosis.» But Borgard presents no documentation of this assertion in his paper.

The arcuate transition of the R wave into the ST segment is taken by Uhlenbruch to be a not unimportant criterion of beginning coronary insufficiency. He bases his assumption on the results of studies carried out by Asshauer at his suggestion. Asshauer found saddle-formed ST segments in at least two leads in 131 out of 1540 electrocardiograms (8.5 %). In 92 cases the change was not pronounced (slightly curved ST segments) and of these patients 44 (47.8 %) complained of anginoid phenomena; of the remaining 37 patients with severe changes (markedly arcuate ST segments) 32 (*i. e.*, 86.5 %) had anginoid symptoms. About one-third of the 131 patients presented other signs of cardiac disease (valvular defects, infarction, myocardial degeneration, hypertension, etc.), but of other changes in the electrocardiogram, Asshauer mentions only notching of the QRS complex in several cases, a slight widening of the QRS complex in two cases, and a low QRS complex in 3 cases.

Van Nieuwenhuizen, Hartog & Matthijssen found saddle formed ST segments on 102 out of 5500 curves (*i. e.*, 2 %) but they fail to mention whether the saddle-formed ST segment was seen only in one lead or simultaneously in more leads. Of these patients 45 % had hypertension, 34 % angina pectoris, 26 % cardiac insufficiency and 14 % dilatation of the heart. Altogether 80 % of the patients presented signs of an organic heart lesion, chiefly coronary sclerosis, and in a little over 10 % of the cases the saddle-formed ST segment was attributed to reflex stimulation of the vagus (peptic ulcer) or primary vagal stimulation (angina pectoris in young per-

additional positive wave, an $R^2$ wave (*Fig. IC*), but this may be absent too (Fig. 1D).

As previous authors have paid attention only to saddleformed ST segments after QRS complexes with the S wave lacking, in the following studies a distinction will be made between saddleformed ST segments after QRS complexes without an S wave and after QRS complexes with the S wave preserved.

In the course of 1938, altogether 925 patients were admitted to the Medical Department B of the Rigshospital. In 20 of these cases no electrocardiogram was taken, mostly because the patients died within 24 hours after admission. The remaining 905 patients are distributed over the three groups — patients with normal circulation, patients with potential heart disease, and patients with heart disease — as shown in the following tabulation, which also gives information about the occurrence of saddle-formed ST segments in each of the three groups.

| | No. of patients | Occurrence of saddle-formed ST segments after lacking S wave | Occurrence of all types of saddle-formed ST segments |
|---|---|---|---|
| Patients with normal circulation. | 510 | 224 pts. = 43.9 % of 510 | 260 pts. = 50.9 % of 510 |
| Patients with potential cardiac disease. | 203 | 90 » = 44.3 % » 203 | 107 » = 53.9 % » 203 |
| Patients with heart lesions. | 192 | 66 » = 34.4 % » 192 | 78 » = 40.1 % » 192 |

The frequency of saddle-formed ST segments is very great, namely: 35—45 % if we consider only the saddle-formed ST segments seen after QRS complexes with lacking S waves, and 40—50 % when we reckon also the ST segments occurring after QRS complexes with the S wave preserved.

The reason why saddle-formed ST segments are a little less frequent among patients with cardiac disease than in the two other groups is, that the group of cardiac lesions includes relatively more instances of negative T waves and — according to the criteria of the saddle form — in such cases the ST segments cannot be saddle-

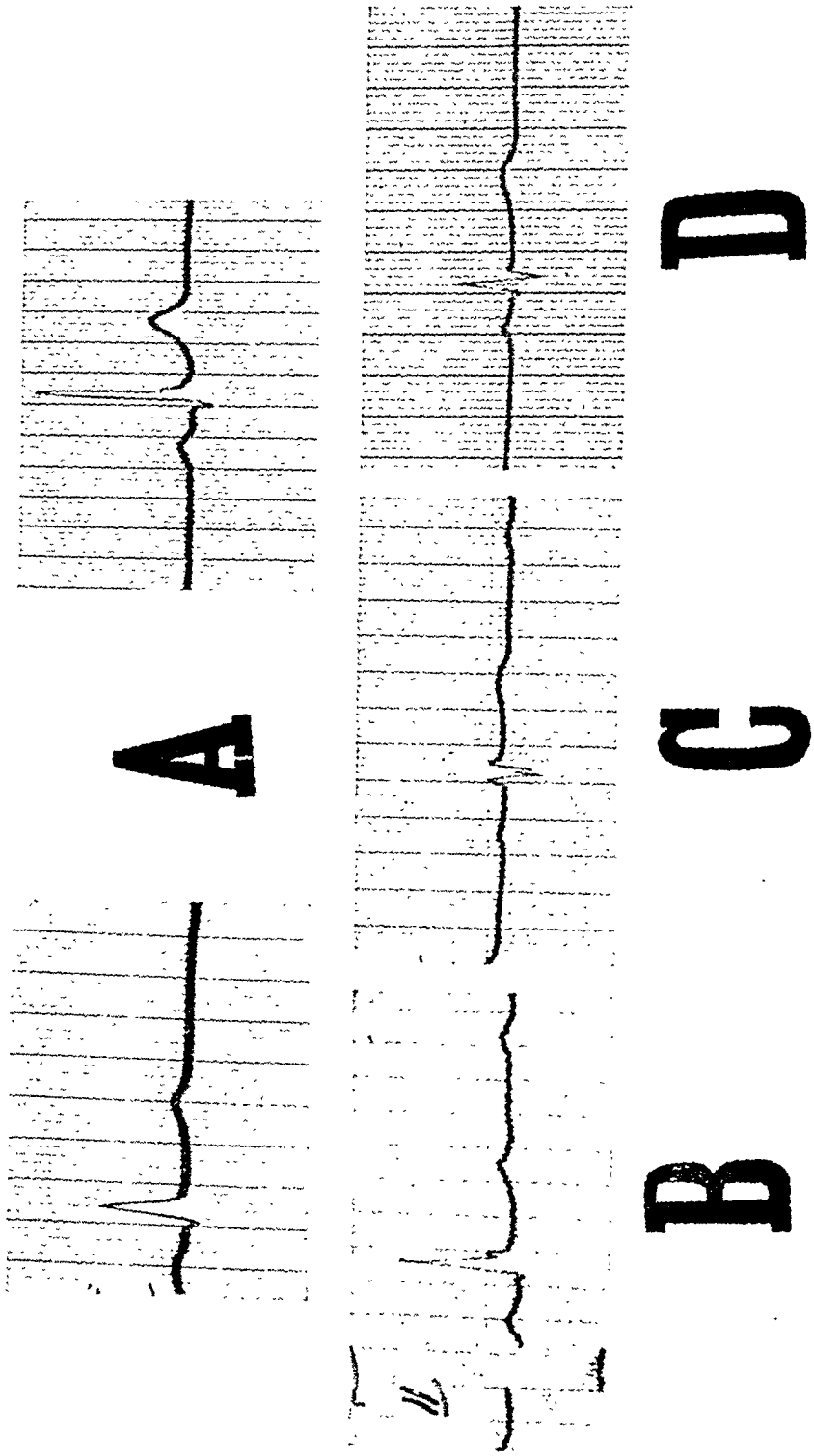



Fig. 1. *A* shows saddle-formed ST segments after QRS complexes with the S wave absent and a smooth transition between the QRS complex and the ST segment; slightly saddle-formed at the left, markedly saddle-formed at the right.
*B* shows a saddle-formed ST segment after a QRS complex with the S wave missing and with a »notch» at the transition.
*C* shows a saddle-formed ST segment after a QRS complex with the S wave preserved and another positive wave.
*D* shows a saddle-formed ST segment after a QRS complex with the S wave preserved and without any other positive wave.
Time marker 0.02 and 0.10 sec.

formed. So the frequency of saddle-formed ST segments is really the same in all three groups of patients, and consequently the occurrence of saddle-formed ST segments cannot be of any importance to the diagnosis of heart lesions — at any rate not when the consideration of the question, as done in the tabulation above, includes the cases in which the saddle form occurs only in a single derivation.

It then remains to look into the question whether the simultaneous occurrence of saddle-formed ST segments in Leads I and II (Borgard) or at least in two derivations (Asshauer) is of diagnostic importance, and also the significance of a particularly pronounced saddle form (Asshauer).

The distribution in the various leads of saddle-formed ST segments after QRS complexes with absence of the S wave is shown in Table 1, and the distribution of all types of saddleformed ST segments is given in Table 2. From Table 1 it will be noticed that saddle-formed ST segments after QRS complexes with absence of the S wave occurred simultaneously in Leads I and II in 40 patients, with normal circulation, in 14 patients with potential heart lesions, and in 14 patients with cardiac disease. The percental frequency of this change in the three groups is then found to be respectively: 7.8 % (40 out of 510), 6.9 % (14 out of 203), and 7.3 % (14 out of 192). For all types of saddle-formed segments (Table 2) the corresponding percentages are: 10.4 % (53 out of 510), 9.9 % (20 out of 203), and 10.4 % (20 out of 192). So, also the simultaneous occurrence of saddle-formed ST segments in Leads I and II is of no diagnostic significance.

Saddle-formed ST segments after QRS complexes with absence of the S wave (Table 1) occurred simultaneously in at least two leads (only derivations from the extremities are taken into account) in 93 patients with normal circulation, 33 patients with potential heart lesions and 18 patients with cardiac disease. The percental frequency of this phenomenon in the three groups is then found to be respectively: 18.2 % (93 out of 510), 16.3 % (33 out of 203), and 9.4 % (18 out of 192). The corresponding percentages for all types of saddle-formed ST segments (Lead II) are then: 23.3 % (119 out of 510), 22.2 % (45 out of 203), and 16.1 % (31 out of 192). So, also the simultaneous account of saddle-formed ST segments in at least two leads can be considered diagnostically insignificant.

**Table 1.**

*Distribution of Saddle-formed ST Segments after QRS Complexes with Absence of the S Waves in the Various Leads.*

| Saddle-formed ST segments in Leads | I, II and III | I and II | I and III | II and III | I | II | III | Simultaneous in precordial and extremity derivations | In precordial leads alone |
|---|---|---|---|---|---|---|---|---|---|
| Patients with normal circulation | 15 | 25 | 0 | 53 | 67 | 38 | 26 | 46 | 0 |
| Patients with potential cardiac disease | 4 | 10 | 0 | 19 | 27 | 21 | 9 | 15 | 0 |
| Patients with heart disease | 3 | 11 | 0 | 4 | 25 | 20 | 3 | 22 | 0 |

**Table 2.**

*Distribution of all Forms of Saddle-formed ST Segments in the Various Leads.*

| Saddle-formed ST segments in Leads | I, II and III | I and II | I and III | II and III | I | II | III | Simultaneous in precordial and extremity derivations | In precordial leads alone |
|---|---|---|---|---|---|---|---|---|---|
| Patients with normal circulation | 20 | 33 | 0 | 66 | 64 | 40 | 31 | 85 | 6 |
| Patients with potential cardiac disease | 5 | 15 | 0 | 25 | 30 | 18 | 14 | 23 | 0 |
| Patients with heart disease | 3 | 17 | 0 | 11 | 24 | 17 | 5 | 30 | 1 |

Only in 19 of our patients could the ST segments reasonably be characterized as markedly saddle-formed. Of these 19 patients, 12 were circulatorily healthy, 6 had potential heart lesions, and 1 patient had cardiac disease. The number of patients in this group is small, it is true, but considering our other results concerning the diagnostic significance of the saddle-formed ST segments, we do not think that it requires a larger material to establish that also the markedly saddle-formed ST segments are of no diagnostic significance.

With one exception, the aforementioned investigators have emphasized that saddle-formed ST segments constituted a sign of beginning coronary sclerosis or coronary insufficiency. One might imagine, then, that the frequency of saddle-formed ST segments in

our material were due to the circumstance that this material consisted chiefly of older patients who presented just this electrocardiographic change as the only evidence of sclerotic changes in the coronary arteries. In our material, only 34.1 % of the patients (309 out of 905) were over 50 years old. The distribution of these patients in the various groups is shown in the following tabulation, in which we have considered only the cases with saddle-formed ST segments after QRS complexes in which the S wave was absent.

| | | | | | |
|---|---|---|---|---|---|
| *Patients with normal circulation.* | Over 50 years | Saddle form in | 52 of | 93 | = 55.9 % |
| | Under 50 » | » » | » 172 » | 417 | = 41.3 % |
| | | | Difference | | = 14.6 % |
| | | (Mean error of | » | | = ± 5.69 %). |
| Patients with potential cardiac disease | Over 50 years | Saddle form in | 46 of | 95 | = 48.4 % |
| | Under 50 » | » » | » 43 » | 108 | = 39.8 % |
| | | | Difference | | = 8.6 % |
| | | (Mean error of | » | | = ± 6.96 %). |
| Patients with heart lesions | Over 50 years | Saddle form in | 43 of | 121 | = 35.5 % |
| | Under 50 » | » » | » 24 » | 71 | = 33.8 % |
| | | | Difference | | = 1.7 %. |

At a mere glance these figures appear to show that saddle-formed ST segments are a little more frequent in patients with normal circulation over 50 years than in the category of patients under 50, the difference in the percental frequency for the two age-classes being 14.6 %. But this value is only about 2 ½ times the mean error of the difference (± 5.69 %), so that the difference is not statistically tenable. The frequency of saddle-formed ST segments in the group of patients with a normal circulation under 50 years is 41.3 %, while the frequency for the entire group, as recorded before, is 43.9 % (224 out of 510). From this, it is evident that the possibly slightly increased frequency of saddle-formed ST segments in the patients over 50 years has influenced the frequency of such segments in the entire group but slightly.

Finally, Table 3 shows the frequency of the various types of saddle form and their distribution on the individual leads. Only 12 patients (with saddle-formed ST segments in 21 leads) had received

Table 3.

*Frequency of the Various Types of Saddle Form and Their Distribution in the Individual Leads.*

| Leads | I | II | III | *d* | *s* | Total | |
|---|---|---|---|---|---|---|---|
| Saddle form after QRS complex with absence of S wave; smooth transition.. | 170 | 187 | 117 | 3 | 66 | 543 | 636 |
| Saddle form after QRS complex with absence of S wave and »notch» in the transition..... | 17 | 33 | 18 | 7 | 18 | 93 | |
| Saddle form after QRS complex with preserved S wave and an $R^2$..... | 16 | 37 | 37 | 9 | 48 | 147 | 188 |
| Saddle form after QRS complex with preserved S wave and no $R^2$ ..... | 7 | 11 | 4 | 7 | 12 | 41 | |

digitalis. Hence digitalis therapy cannot have been the cause of the great frequency of saddle-formed ST segments in the present material. Saddle-formed ST segments are more frequent in the derivations from the extremities than in the precordial derivations *d* and *s*, and most frequent in Lead II. The reason for the rather rare occurrence of saddle-formed ST segments in Lead *d* is the fact that this lead, as a rule, gives a large S wave. It will be noticed, too, that saddle-formed ST segments after QRS complexes with absence of the S wave is far more frequent than similar segments after QRS complexes with presence of the S wave (636 times against 188), and that in the latter group the saddle form most often is associated with the presence of a second R wave, an $R^2$.

## Discussion.

The frequency of the saddle-formed ST segments in the material here presented is considerably greater than encountered in all previous materials. This is not only due to the fact that in our account we have reckoned all the cases too, in which the ST segment was saddle-formed merely in one lead. Asshauer, for instance, found saddle-formed segments in at least two leads in 131

out of 1540 patients, that is, in 8.5 % of his cases. We have found saddle-formed ST segments in at least two leads in 144 out of 905 cases, i. e., in 15.9 %, and in view of the size of the materials, this difference in frequency is statistically tenable. The cause of this difference is to be looked for in the estimation of the electrocardiograms. We have kept strictly to the criteria of saddle form given above, and we have taken into account all cases in which the ST segment took a slanting course immediately after its departure from the QRS complex, even though the convexity of the ST segment on the whole was pronounced but little. This, we think, is absolutely necessary; to distinguish between different grades of saddle form can result only in a clinically jeopardizing subjectivity. In a previous investigation, Kaj Larsen & Skúlason found saddle-formed ST segments in 22 out of 100 normal persons, which is considerably below the frequency of saddle-form ST segments in the group of circulatorily healthy patients in the present material. The reason for this difference is the fact that the criteria adopted by Kaj Larsen & Skúlason for saddle form have not been sufficiently clear-cut. A revision of their material on the basis of criteria for saddle form given in the present paper shows that saddle-formed ST segments after QRS complexes with absence of the S wave occurred in 34 out of 100 experimental subjects, and saddle-formed ST segments after all types of QRS complexes occurred in 39 out of 100 experimental subjects. And these frequencies are not statistically different from the frequencies of saddle-formed ST segments in the circulatorily healthy patients of the present material.

Besides the clinical studies mentioned above, Van Nieuwenhuizen, Hartog & Matthijssen have presented some theoretical arguments in favor of the diagnostic significance of the saddle-formed ST segments. They emphasize that the electrical axis or vector during the tracing of the saddle-formed ST segments rotates in the same direction as the hand of the clock — just as in the tracing of the deep $Q_{III}$ wave described by Pardee — and, without giving particular reasons, they take this fact to prove or indicate that saddle-formed ST segments are of similar significance as Pardee's $Q_{III}$. We fail to see the justification of this view, and we further wish to call attention to the following: It is true that the vector rotates with the hand of the clock in the registration of the ST segments when these are saddle-formed in at least two of the deri-

vations from the extremities but this will not always hold true when the saddle form is encountered only in one lead. Further, the vector may rotate with the hand of the clock also in the graphical registration of quite normal ST segments — for instance, in upward inclining ST segments in Leads I and II, when $ST_{II}$ is ascending more abruptly than $ST_I$.

A few authors have suggested that saddle-formed ST segments are artefacts brought about through incapacity of the amplifying electrocardiographs for correct registration of the electrocardiogram. We agree with Asshauer in considering most of the amplifiers now put on the market to be so good that this possibility can be disregarded, and we know that this applies to the model of apparatus employed by us.

## Summary.

Saddle-formed ST segments are equally frequent in normal persons, patients with normal circulation, patients with potential heart lesions and patients with cardiac disease, and hence they are of no diagnostic significance. This applies also to the simultaneous occurrence of saddle-formed ST segments in Leads I and II (Borgard) and to the simultaneous occurrence of saddle-formed ST segments in at least two leads (Asshauer) as well as to particularly pronounced saddle-formed ST segments (Asshauer).

In the material presented by the authors, comprising altogether 905 patients admitted in succession to a medical clinic, the frequency of saddle-formed ST segments (after QRS complexes with absence of the S wave) was 35—45 %. The reason for this high frequency cannot be looked for in the age of the patients or in frequent employment of digitalis; it has to be looked for exclusively in a consistent employment of the given criteria for saddle form.

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# Studies on the electrocardiographic diagnosis of acute and fibrous infarction of the heart, on the basis of 51 cases with autopsy.[1]

## I. Introductory Remarks. Solitary Infarcts.

By

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The electrocardiographic changes in cardiac infarction are now elucidated so well that it is practicable in many cases to make the diagnosis cardiac infarction and establish its localization by means of the electrocardiographic changes alone. As shown by Parkinson & Bedford (9, 10), and by Barnes & Whitten (1, 2) and confirmed through numerous investigations, the two most frequent types of cardiac infarction, infarcts of the anterior wall and the posterior wall, are associated with quite definite types of electrocardiographic changes designated as Type $T_1$ and Type $T_3$. Also the QRS complex often shows characteristic changes in the two types of cardiac infarction — as pointed out by Pardee (8), Wilson and collaborators (13), Durant (3), and Winternitz (12). In the last decade, finally, several authors have demonstrated that the derivations from the extremities often fail in anterior wall infarction and that precordial leads here are of great importance to the electrocardiograph diagnosis [*e. g.*, Wolferth & Wood (16), Wilson and collaborators (14, 15), Jervell (5), Holzmann (4), Vagn Mortensen (7)].

[1] The studies here presented were carried out with the aid of a grant from P. Carl Petersen's Fond.

Although there can be no doubt that many instances of cardiac infarction present one of the mentioned characteristic types of electrocardiographic changes, it is an unquestionable fact that in the clinic we often meet with cases of cardiac infarction showing uncharacteristic changes in the electrocardiogram, or changes that are even conflicting as to the location of the infarct. This is due to the circumstance that the established electrocardiographic types correspond to clear-cut, typical cases of cardiac infarction and that these features are found in only a part of the patients examined. As coronary thrombosis most often arises on the basis of a chronic arteriosclerotic heart lesion, the pathologic-anatomical picture may naturally be highly variable. Thus there may be a severe sclerosis of the other arteries and more or less diffuse fibrosis of the myocardium or old infarcts resulting from earlier occlusions of the coronary arteries. Such occlusions may also give rise to variations in the areas supplied by the different arterial branches, as other arteries and new-developed collaterals take up the blood supply of the fields in which the arteries are affected most severely. All told, it may safely be said that the conditions actually met with often deviate considerably from the »ideal» conditions on which the appearance of quite schematic electrocardiographic changes is dependent.

For elucidation of the value of the electrocardiograms to the diagnosis and localization of a cardiac infarct, in this and a subsequent paper I shall present autopsy material from the Medical Department B of the Rigshospital. [1]

The terminology is still somewhat unsettled as the designation »cardiac infarct» often is employed for the acute infarction alone. Hence it is to be emphasized explicitly that in this work the term »cardiac infarction» covers not only the acute infarct but also its sequela: the chronic or fibrous infarct.

## Material.

On going through the autopsy records from Dep. B for the period of 1/1, 1936 to 30/6, 1941, it was found that autopsy had revealed an acute or fibrous cardiac infarction in 51 cases. As to the localization of the infarction, the distribution of these cases is as follows:

[1] I am indebted to Professor J. Engelbreth-Holm for permission to make use of the autopsy records.

| | | |
|---|---|---|
| 1) Anterior wall infarction | 12 | cases. |
| 2) Posterior » » | 7 | » |
| 3) Lateral infarction | 2 | » |
| 4) Anterior + posterior wall infarction | 20 | » |
| 5) Other combinations and poorly defined processes | 10 | » |

The first three groups are made up of cases in which the autopsy revealed only a single infarct, even though the infarct extended to other parts of the myocardium besides the anterior, posterior, or lateral wall, respectively. The last two groups are made up of cases showing several infarcts at the same time.

In a few cases the records mention merely the presence of an infarct in the left ventricle, without stating whether it was located in the anterior wall or in the posterior. Such cases are rubricated after the occluded artery. The same applies to a few acute cases taking a rapid, fatal course in which the autopsy revealed a completely occluding fresh thrombosis but no infarct, presumably because infarction had not yet had time to develop. Such cases are reckoned as infarction and rubricated after the occluded artery.

## Electrocardiograms.

Five patients died so soon after the admission that no electrocardiogram could be taken. The remaining 46 patients were electrocardiographed, most of them several times. Altogether 419 electrocardiograms were taken of these patients, 384 of them in precordial leads as well as derivations from the extremities.

The precordial leads are in most of the cases the Leads *d* and *s* introduced by Kaj Larsen (6). In Lead *d* the different electrode is located at the apex of the angle between the left costal margin and the ensiform; in Lead *s* the different electrode is placed 4 cm to the left of the ictus and at this level. The indifferent electrode is placed on the right arm. The latest electrocardiograms were taken in Leads $CR_2$ and IVR, in which the different electrode is placed respectively in the 4' left intercostal space, immediately to the left of the sternum, and over the ictus, while the indifferent electrode is placed on the right arm.

In the description of the electrocardiograms mention is made of various abnormalities for which the following criteria are adopted:

*Large* $Q_1$: $Q_1 \geqq 1$ mm and larger than 1/5 of the largest R wave.

*W-formed* $QRS_1$: Same criteria as for W-formed $QRS_2$ (see below) and first deflection meeting the criteria for large $Q_1$.

*Winternitz Type I:* Small $R_1$ together with large $S_2$ and $S_3$.

*Winternitz Type II:* Negativity of the main deflection in QRS in all 3 leads.

*Winternitz Type III:* Diminution of the main deflections in all 3 leads, while the minor deflections remain unchanged, so that the result is an electrocardiogram with small notched QRS complexes ($\leqq 5$ mm) in all three leads.

*M-W-formed $QRS_2$:* All deflections $\leqq 5$ mm; all deflections respectively over or under the isoelectric level; QRS at least 0.08 sec. wide.

$Q_2$: $Q_2 \geqq 1$ mm.

*Large $Q_3$*: $Q_3$ is the initial deflection, followed by an R wave which is not followed by any S wave; and $Q_3$ must measure at least ¼ of the largest R wave in derivations from the extremities. Cases with right preponderance or deeply notched $QRS_3$ are exempted from this rule.

*Durant $QRS_3$:* Completely negative $QRS_3$ making up at least ¼ of the largest R wave in derivations from the extremities, and appearing together with a large $Q_2$ or sign of posterior wall infarction in RS-T and/or T.

*RS-T elevated:* RS-T 1 mm or more above the isoelectric level.

*RS-T depressed:* RS-T 1 mm or more below the isoelectric level.

*Coronary T:* Only negative coronary T's are reckoned; the form must be typical. Still, less typical T inversions are reckoned, too, if they are preceded by elevation of RS-T.

These electrocardiographic anomalies have been described by various investigators as being common in cardiac infarction and rare in other heart lesions, so that considerable diagnostic significance may be assigned to them. Thus the various types of cardiac infarction involve respectively the following electrocardiographic abnormalities:

*QRS changes of anterior wall type:* Large $Q_1$, W-formed $QRS_1$, Winternitz Types I and II.

*RS-T and T changes of anterior wall type:* Elevation of RS-$T_1$ (sometimes also of RS-$T_3$), depression of RS-$T_2$, later absence of RS-T deviations and development of negative coronary $T_1$ (sometimes also $T_2$) and positive $T_3$.

*QRS changes of posterior wall type:* Large $Q_3$, Durant $QRS_3$.

*RS-T and T changes of posterior wall type:* Depression of RS-$T_1$, elevation of RS-$T_3$ (sometimes also of RS-$T_2$), later absence of RS-T deviation and development of positive $T_1$ and negative coronary $T_3$ (sometimes also $T_2$).

*Winternitz Type III* is described as being characteristic of anterior as well as posterior wall infarction as a result of two thromboses. M—W-formed $QRS_2$ is described as being characteristic of coronary lesions.

The diagnostic value of the various abnormalities is increased considerably by a combination of the QRS changes with the corresponding RS-T changes. This has been emphasized in particular by Durant (3) who demonstrated, among other things, that a large $Q_3$ combined with a $Q_2$ and negative $T_2$ and $T_3$, but positive $T_1$, allows the diagnosis posterior wall infarction with almost 100 % certainty.

When the size of the deflections is given in mm, it is taken for granted that 1 mV = 10 mm.

For illustration of various cardiographic abnormalities, in Figs. 1 and 2 an electrocardiogram is shown from each of the cases of anterior wall infarction (and one case of lateral infarction). It is to be emphasized that these illustrations and the description of the electrocardiographic changes given in the following need not necessarily be congruous. For the description covers all the changes observed in the respective case at some point of time or other, while the illustration shows only a single electrocardiogram in each case.

## Group of Solitary Anterior Wall Infarcts.

The group comprises Cases 1—12, a record of which is given schematically in Table 1.

*Autopsy Findings.* — In 5 cases (1, 2, 3, 9 and 10) the infarct occupied some part of the anterior wall, apex and anterior lower part of the septum. In one of these cases (3) also the margo obtusus was infarcted, as the thrombosis was located at such a high level that also the left circumflex branch was deprived of its blood supply; and in two of the cases (9 and 10) parts of the posterior wall were infarcted, too.

In 3 cases (8, 11 and 12) the infarction involved the anterior wall, apex and lower part of the posterior wall; in 1 case (6) the apex and lower part of the posterior wall; and in 1 case (7) only the anterior wall.

The 2 remaining cases (4 and 5) presented some features of particular interest. In both cases, death came a few hours after the appearance of the occlusion, and the anterior descending branch was completely occluded by thrombosis. In one case (4) no infarction could be demonstrated, however, neither macroscopically nor microscopically. In the other case (5) the anterior wall was the site of a rupture, measuring 3—5 cm in length, but the additional morbid changes were very limited. Both cases illustrate that it takes a certain length of time after the occlusion of the artery before the infarction is established. The latter case further shows that rupture may take place in direct connection with the occlusion of the coronary artery, as emphasized recently by Worsaae (17). Most often, however, rupture does not take place until some days after the occlusion, at a point of time when a soft infarct has developed in the ventricular wall.

Among these 12 cases the infarction was recent in 8, recent and fibrous changes were seen in 2, and fibrous changes alone in 2. Rupture

## Table 1.

*Electrocardiographic Changes in 12 Cases of Anterior Wall Infarction (1—12), 7 Cases of Posterior Wall Infarction (13—19) and 2 Cases of Lateral Infarction (20—21).*

| Case No. | Record No. | Date of attack | No. of ECG. | Dates of electro-cardiograms | Date of death | Large $Q_1$ | W-formed $QRS_1$ | Wintemitz I | Wintemitz II | Wintemitz III | M-formed $QRS_2$ | W-formed $QRS_2$ | $Q_2 \geqq 1$ mm. | Large $Q_3$ | Durant $QRS_3$ | RS-$T_1$ elevation | RS-$T_1$ depression | RS-$T_2$ elevation | RS-$T_2$ depression | RS-$T_3$ elevation | RS-$T_3$ depression | Coronary $T_1$ | Coronary $T_2$ | Coronary $T_3$ | Site of occlusion. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 295/36 | 15/3/36 | 8 | 16/3—27/3/36 | 30/3/36 | + | + | + | — | — | — | — | — | — | — | + | — | + | — | — | + | — | — | — | Ant. descend. branch 1 cm. from aorta. |
| 2 | 577/40 | 5/4/40 | 47 | 9/4—19/7/40 | 28/7/40 | + | — | + | — | — | — | — | — | — | — | + | — | + | — | (+) | + | + | + | + | Ant. descend. branch, upper part. |
| 3 | 749/40 | 17/10/40 | 2 | 18/10—19/10/40 | 20/10/40 | + | — | — | — | — | — | — | — | — | — | + | — | — | + | — | + | + | — | — | Left coronary art., upper part. |
| 4 | 84/41 | 29/1/41 | 2 | 29/1/41 | 29/1/41 | — | — | ? | — | — | — | — | — | — | — | + | — | — | + | — | + | — | — | — | Left coronary art., at bifurcation. |
| 5 | 898/40 | 16/12/40 | 1 | 16/12/40 | 16/12/40 | — | — | — | — | — | — | — | — | — | — | + | — | — | + | — | + | — | — | — | Ant. descend. branch, 1 cm. from depart. |
| 6 | 215/41 | 3/2/41 | 16 | 10/2—16/3/41 | 16/3/41 | — | — | - | — | — | — | — | + | (+) | — | — | (+) | — | — | — | — | + | + | — | Ant. descend. branch at the middle. |
| 7 | 559/38 | 7/7/38 | 14 | 7/7—15/7/38 | 15/7/38 | — | — | — | — | — | — | — | — | — | — | (+) | — | — | (+) | — | (+) | — | — | — | Ant. descend. branch, 2 cm. from depart. |
| 8 | 267/37 | 10/3/37 | 5 | 18/3—23/3/37 | 24/3/37 | — | — | - | — | — | — | + | + | — | + | — | — | + | — | + | — | — | — | — | Ant. descend. branch. at the middle. |
| 9 | 162/41 | 17/2/41 | 8 | 18/2—27/2/41 | 27/2/41 | — | — | — | — | + | — | + | + | + | + | — | — | + | — | + | — | + | + | + | Ant. descend. branch, 3½ cm from depat. |

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 734/36 | 15/9/36 | 1 | 16/9/36 | 16/9/36 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | Ant. descend. branch, 2—3 cm fromaorta. |
| 11 | 508/37 | 1931? | 5 | 21/5—5/6/37 | 13/6/37 | — | — | — | — | — | + | — | — | — | — | — | (+) | — | (+) | — | — | — | — | — | Ant. descend. branch, distal half. |
| 12 | 68/41 | ? | 0 | 0 | 24/1/41 | | | | | | | | | | | | | | | | | | | | Ant. descend. branch, 4 cm. from depart. |
| 13 | 1004/38 | Nov. 38 | 6 | 5/12—20/12/38 | 21/12/38 | — | — | — | — | — | — | — | + | + | — | — | + | — | — | + | — | — | + | + | Right coronary art., 3 cm from depart. |
| 14 | 37/41 | Aug. 40 | 24 | 10/6—16/12/40 | 13/1/41 | — | — | — | — | — | — | — | + | — | + | — | — | — | — | — | — | — | + | + | Coronary arteries narrow, partly occluded. |
| 15 | 376/39 | ? | 20 | 22/3—20/4/39 | 28/4/39 | — | — | — | — | — | — | — | — | + | — | — | (+) | — | (+) | — | — | — | — | — | Right coronary art., distal part. |
| 16 | 985/39 | ? | 2 | 26/11—27/11/39 | 25/12/39 | — | — | — | — | — | — | — | + | + | — | — | — | — | — | — | — | — | — | — | Right coronary art., peripherally. |
| 17 | 159/40 | ? | 11 | 18/1—1/3/40 | 4/3/40 | — | — | — | — | — | — | — | — | + | — | — | — | — | — | — | — | — | — | — | Right coronary art., 4 ½ cm from depart. |
| 18 | 497/40 | 6/1/38 | 11 | 16/5—25/6/40 | 27/6/40 | — | — | — | — | + | + | + | + | — | + | — | — | — | — | (+) | — | — | — | — | Right coronary art., 3 cm from depart. |
| 19 | 717/37 | 4/10/37 | 0 | 0 | 4/10/37 | | | | | | | | | | | | | | | | | | | | Right coronary art., 1—2 cm from depart. |
| 20 | 309/40 | ? | 8 | 8/12/39-22/1/40 | 12/4/40 | — | — | — | — | - | - | - | + | + | - | — | (+ | — | — | (+ | — | — | — | — | Left circumflex branch, just after depart. |
| 21 | 897/38 | 25/11/38 | 0 | 0 | 25/11/38 | | | | | | | | | | | | | | | | | | | | Left coronary art., just after depart. |

+ means that the electrocardiographic abnormality was found in one or more of the electrocardiograms taken.

(+) means that the abnormality was present but probably not due to the infarction.

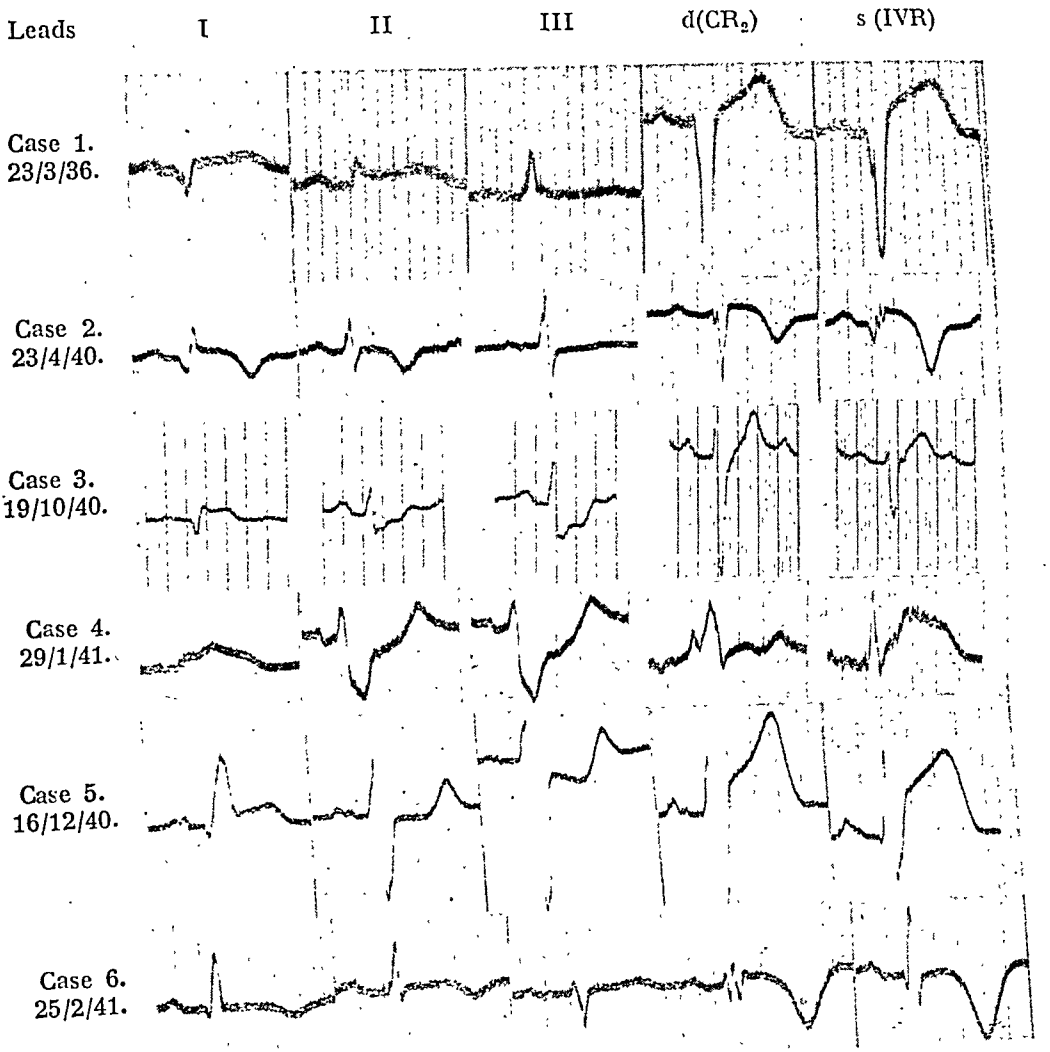



Fig. 1. An electrocardiogram from each of Cases 1—6 (solitary anterior wall infarcts) taken in three derivations from the extremities and two precordial leads. In Cases 4 and 6 the precordial leads $CR_2$ and IVR are employed; in the other cases, Leads *d* and *s*.

For description and interpretation of the changes, see the text.

was found in 2 cases (5 and 9), aneurysm in 1 case (12). Pericarditis was described in 6 cases.

The autopsy records permit no other estimation of the localization and extension of the infarcts than the data already mentioned. On the other hand, as is evident from Table 1, precise information is given about the site of the occlusion in the anterior descending branch. This is highly variable and, in connection with the above data on the

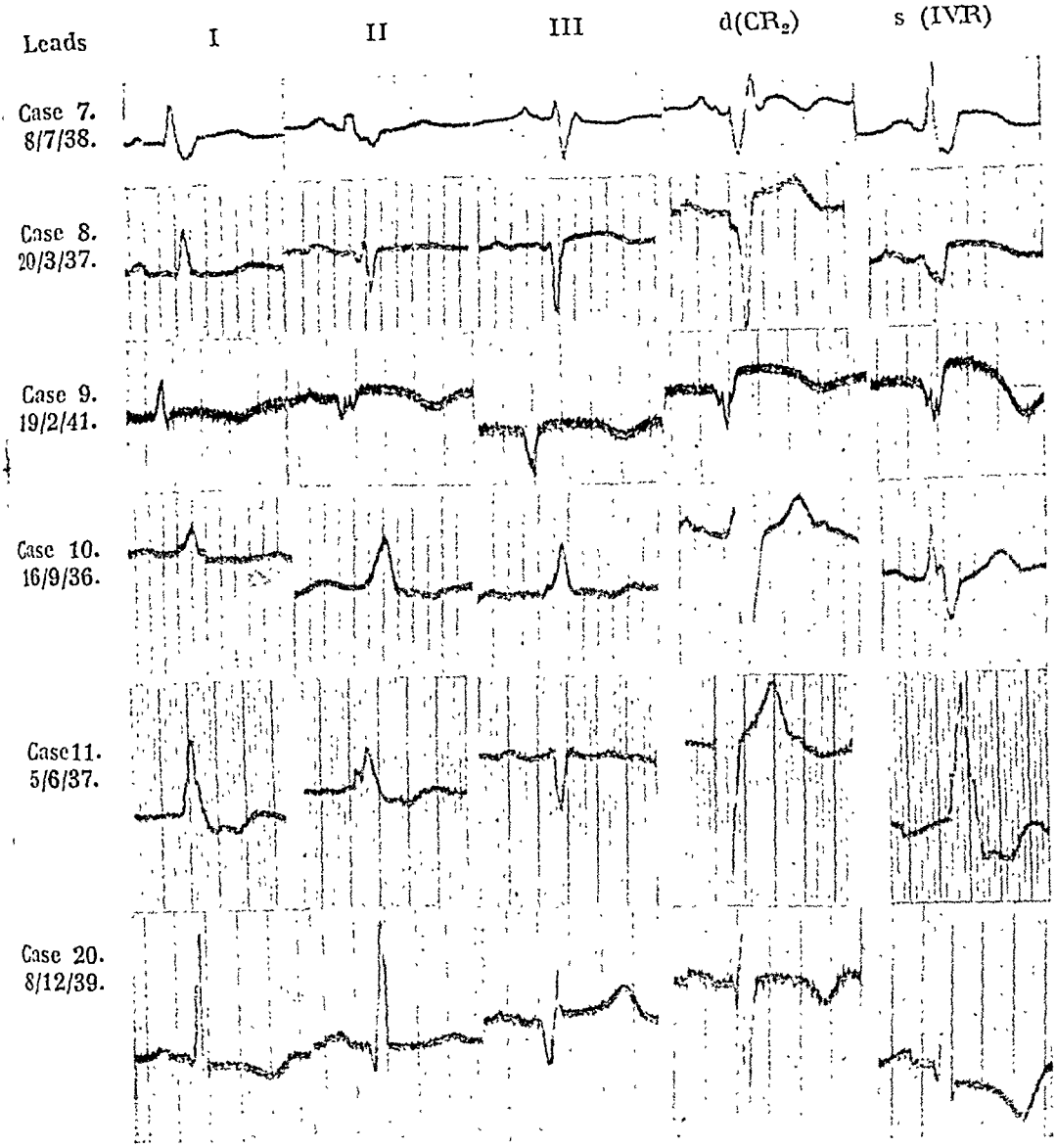



Fig. 2. An electrocardiogram from each of Cases 7—11 (solitary anterior wall infarcts) and from Case 20 (lateral infarct). In Case 9 the precordial leads $CR_2$ and IVR are employed; in the other cases, leads *d* and *s*. For description and interpretation of the changes, see the text.

infarcts, it shows that the *pathologic-anatomical picture resulting from an occlusion in the anterior descending branch is subject to q ite considerable variation.*

*Electrocardiograms.* — Altogether 109 electrocardiograms were taken in this group of cases, but only 11 of the patients were examined in this way. Table 1 gives the data on the occurrence of the above-

mentioned electrocardiographic abnormalities in each of these cases. All the electrocardiograms taken were pathological, but some of them showed unspecific changes that could not be entered in this tabulation; apart from disturbances of conduction and arrhythmia, these changes will not be mentioned further as they were so ordinary that they might be said a priori to be of no interest to the diagnosis of infarction.

As seen from Table 1, *QRS changes* of the anterior wall type were found in only 4 out of the 11 cases. A large $Q_1$ was found in 3 cases (in respectively, 8, 20 and 1 of the electrocardiograms taken); in one of the cases this feature was associated with W-formed $QRS_1$ (in 7 of the electrocardiograms taken), and in 2 it was combined with Winternitz Type I (in respectively 1 and 21 of the electrocardiograms taken). In 1 case (4), the electrocardiograms showed Winternitz Type I (in both the tracings taken), but no $Q_1$.

In 1 of the cases showing QRS changes of anterior wall type (Case 2), these changes were replaced by unspecific QRS changes 5 weeks after the attack; in 1 case (3), the typical QRS changes did not appear till 2 days after the attack; and in the remaining 2 cases (1 and 4) the typical QRS changes were present in all the electrocardiograms taken.

Of the 11 cases 3 showed also QRS changes of the posterior wall type (6, 8 and 9). In Case 6, however, these changes could not be put in relation to the cardiac infarction, as they were found only in the last tracing, taken immediately before death and consisting in a large $Q_3$ and a $Q_2$, which together with a large $S_1$ and typical RS-T changes were suggestive of pulmonary embolism —a diagnosis that was verified on autopsy. In the two other cases (8 and 9) there was a $Q_2$ and a completely negative $QRS_3$ (though one of the tracings in Case 9 showed Pardee $Q_3$), which changes, according to Durant, may be classified together with $Q_2$ and large $Q_3$.

W-formed $QRS_2$ was seen in some of the electrocardiograms from Cases 8 and 9, whereas M-formed $QRS_2$ was not observed. Winternitz Type II was not seen, and Type III was found only in 1 case (9), in which the changes appeared immediately after rupture.

As to *RS-T and T*, 8 out of the 11 cases (1—7 and 9) showed changes of anterior wall type. In 2 of these cases (7 and 9), the changes were so slight, however, that they did not permit the diagnosis of anterior wall infarction. 5 cases (2, 6, 8, 9 and 11) showed changes of posterior wall type, but only in 3 of the cases (2, 8 and 9) could they be

attributed to the infarction, as in one case (6) they were due to pulmonary embolism and in one case (11) to left preponderance of the Rykert-Hepburn (11) type (left preponderance with *depressed* $RS—T_1$ and negative $T_1$ and with *elevated* $RS—T_3$ and positive $T_3$). The 3 cases in which the changes had to be attributed to infarction showed: In Case 2, a coronary $T_3$ in the first electrocardiogram taken, presumably due to previous anterior wall infarction with extension to the apex (and posterior wall ?); in Case 8, a slight elevation of RS-$T_2$ and RS-$T_3$; and in Case 9, a fine coronary T in Leads II and III (but also a negative $T_1$). It is to be noted that the last two cases, as mentioned above, showed also QRS changes of the posterior wall type.

*Precordial Leads.* — In 4 cases (1, 2, 8 and 9), the QRS complex was completely negative, sometimes with a little notch in both precordial leads, while in other electrocardiograms the QRS complex in the parasternal lead was preceded by a small initially positive deflection (often merely a suggestion and nearly always lower than 2 mm), and in some electrocardiograms the initial negative main deflection was followed by an R wave.

In 4 other cases there were small initial R waves, namely: in one case (3) an $R < 2$ mm in Lead *s*; in one case (6) a small, deeply notched, preponderantly negative QRS complex in the parasternal lead, and a normal QRS complex with a small Q wave in the apical lead; in one case (7), the parasternal lead gave a small initially positive deflection, followed by a large negative deflection, which again was followed by a positive deflection, while the apical lead gave an R wave nearly 10 mm in height, besides Wilson block. Finally, one case (10) showed an $R < 10$ mm in Lead *s*.

Case 11 showed a small initial $R_d$, which presumably was due to marked left preponderance; and also the two remaining cases (4 and 5) showed merely unspecific QRS changes or none at all.

*RS-T* and *T* showed changes suggestive of anterior wall infarction in all the cases but three (3, 10 and 11). No case showed any changes suggestive of posterior wall infarction.

*Diagnostic Value of Electrocardiograms.* — In 6 of the 11 cases (1—6) anterior wall infarction could be diagnosed by means of derivations from the extremities alone; in 2 cases (8 and 9) one would be inclined, by means of these derivations alone, to diagnose poste-

rior wall infarction (in Case 9, perhaps anterior + posterior wall infarction); and in 3 cases (7, 10 and 11) the infarction could not be diagnosed from the electrocardiograms. Even taking into account that typical QRS changes might have appeared in Case 5 if an infarct had had time to develop, these findings confirm the view advanced in a previous paper: *that derivations from the extremities will fail in about one-half of all cases of anterior wall infarction in the chronic stages.*

That anterior wall infarction may give posterior wall anomalies in derivations from the extremities, has been pointed out in a previous paper (7), in which 3 cases of this type were described (Cases 32, 33 and 34 in the report mentioned), showing quite similar electrocardiographic changes and autopsy findings as Cases 8 and 9 in this paper. In these cases we are dealing with infarcts occupying the lower part of the anterior wall, the apex and sometimes the lower part of the posterior wall — infarcts produced by a rather peripheral occlusion of the anterior descending branch of the coronary artery.

As will be noticed from Table 1, the infarcts which gave typical QRS changes in the extremity leads were brought about by occlusion of the anterior descending branch in its upper part, whereas the occlusion was more peripheral in most of the other cases. Very likely, then, typical QRS changes makes their appearance in derivations from the extremities only when a considerable part of the anterior wall is infarcted.

In the present material the precordial leads show less typical changes than were seen in Leads $CF_2$ and IVF in a material reported previously. Nevertheless, they are of great diagnostic value. While the diagnosis anterior wall infarction could be made from the extremity leads only in 6 out of the 11 cases, the diagnosis could be made in 9 out of the 11 cases by means of extremity + precordial leads. In particular it is to be pointed out that two of these cases (8 and 9), which from the extremity leads would be diagnosed as posterior wall infarction, are plainly revealed by the precordial leads to be anterior wall infarcts.

## Group of Solitary Posterior Wall Infarcts.

The cases are entered in Table 1 (Cases 13—19). In 5 of the 7 cases the diagnosis was made only on autopsy — in contrast to the preceding group, in which the diagnosis infarction was made prior to the autopsy in every case. Presumably this is connected with the fact that 10 of the anterior wall infarcts were fresh, whereas only 2 of the posterior wall infarcts were fresh.

*Autopsy Findings.* — In 3 cases (14, 16 and 17) the infarct was found in the posterior wall of the left ventricle. In 2 cases (15 and 18), in the posterior wall and the posterior part of the septum; in 1 case (13) a large infarct (5 × 1.5 cm) occupied the greater part of the posterior wall, extending down to the apex (the lumen of the anterior descending branch was greatly reduced); finally, also this group included one case (19) with fresh thrombosis (of the right coronary artery) but without any macroscopic infarction. The patient died within a few hours after the onset of the occlusion.

In 6 cases the occlusion was located in the right coronary artery, but varying greatly in its localization (details given in Table 1). In 1 case (14) the autopsy record merely states that the coronary arteries were partly occluded.

*Electrocardiograms.* — Only 6 of the patients were electrocardiographed. Altogether 74 electrocardiograms were taken.

*QRS complex:* A large $Q_3$ was found in 4 cases, in 3 of these (13, 15 and 16) in all the electrocardiograms taken, in 1 case (17) only in 1 out of 11 electrocardiograms taken. In 2 of the cases with a large $Q_3$ (13 and 16) the records showed also a $Q_2 \geqq 1$ mm. Of the remaining 2 cases of posterior wall infarction, 1 (14) showed Durant $QRS_3$, *i. e.*, a completely negative $QRS_3$, together with other signs of posterior wall infarction in 18 of the 24 electrocardiograms taken; 1 case (18) showed in 1 out of 11 electrocardiograms taken a W-formed $QRS_2$ and a completely negative $QRS_3$, in other electrocardiograms an M-formed $QRS_2$, and in 3 of the electrocardiograms a Winternitz Type III.

Thus all 6 cases showed QRS changes of posterior wall type although they were very scanty in 2 cases (17 and 18) — even doubtful in the latter of these two cases as perhaps the QRS change

here presented merely a form of marked preponderance of the left side. There were no QRS changes of the anterior wall type.

As to *RS—T and T*, changes of the posterior wall type were seen in 4 cases (13, 14, 15 and 18) but in two of these the changes could not be ascribed to the infarction, as in one case (15) they were probably due to digitalis therapy (depression of RS-$T_1$ and RS—$T_2$), and in the other (18) they were probably due to marked preponderance of the left side (depressed RS—$T_1$ and elevated RS—$T_3$). As in most of these cases we are dealing with old infarcts, without electrocardiograms taken in the acute stage, it is not to be wondered that RS—T deviation was found only in so few cases. But it is worth notice that also coronary T was a rare abnormality, being seen only in two cases (13 and 14) in which electrocardiograms were taken in the acute and subacute stages. As emphasized in a previous paper, also the coronary T is a transitory change which is replaced fairly soon by unspecific T wave.

*Precordial Leads.* — In 2 cases (13 and 18) several of the electrocardiograms showed an R wave $< 2$ mm in the parasternal lead and $< 10$ mm in the apical lead. The latter abnormality was further found in Case 17. Otherwise the measures of the QRS complex fell within the normal limits.

RS—T changes indicative of posterior wall infarction were found only in 1 case (13) and here only in the first electrocardiograms, whereas the later ones showed changes that were rather suggestive of anterior wall infarction (a negative T wave resembling coronary T in both precordial leads. The infarct extended down into the apex.

The other cases showed unspecific RS—T and T changes or none at all.

*Diagnostic Value of the Electrocardiograms.* — In 2 cases (13 and 14) the diagnosis posterior wall infarction could be made with certainty from the electrocardiograms taken in the extremity leads; in Case 16, too, the diagnosis could be made with a considerable degree of certainty on the Q waves present in Leads II and III. In the remaining 3 cases the derivations from the extremities showed changes suspicious of posterior wall infarction, it is true, but they did not allow of any definite diagnosis. The extremity leads showed the most characteristic changes, and the precordial leads offered no additional evidence of diagnostic value.

## Group of Solitary Lateral Infarcts.

The material includes only two cases of clear-out lateral infarcts (20 and 21), and only the first of these was examined electrocardiographically. In both cases the occlusion was located in the left circumflex branch, just below the site of departure. The infarcts were localized respectively to the lateral wall + the left part of the posterior wall of the left ventricle and to the lateral wall.

Electrocardiograms from Case 20 (see Fig. 2) showed depression of RS—$T_1$, negative $T_1$, elevation of RS—$T_3$ and a positive $T_3$ resembling a positive coronary T; in addition there were a $Q_2$ and a large $Q_3$. The precordial leads showed QRS changes of anterior wall type, and also the T changes were of anterior wall type, with the exception of RS—T in Lead s, which was depressed. The RS—T changes in the extremity leads and in Lead *s* are possibly ascribable to marked preponderance of the left side, but this may hardly explain the marked resemblance of $T_3$ to a coronary T, and at any rate it cannot explain the negative $T_d$ nor the QRS complex in Lead *d*. Thus the electrocardiograms show a mixture of anterior and posterior wall changes.

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A subsequent paper will deal with the remainder of the material, the multiple infarcts. Then the work will conclude with a survey of the entire material and the conclusions that may be arrived at from this investigation.

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# Studies on the electrocardiographic diagnosis of acute and fibrous infarction of the heart, on the basis of 51 cases with autopsy.[1]

## II. Multiple Infarcts. Survey of the Entire Material.

By

VAGN MORTENSEN.

(Submitted for publication May 9, 1942).

In continuation of a preceding paper, in which an account is given of the purpose of the present studies, the material in general and the first 21 cases — solitary infarcts — the remaining part of the material — the multiple infarcts — will now be dealt with, and then the work will end with a survey of the entire material.

### Anterior + Posterior Wall Infarction.

The 20 cases included in this group are recorded in Table 1. In 6 of the cases the infarction was diagnosed first on autopsy; in the other cases it was diagnosed ante mortem.

*Autopsy Findings.* — In a few of the cases the description of the autopsy findings was rather vague. In cases 32, 33 and 34, for instance, fibrous or acute changes were noted »in the myocardium» or »in the left ventricle», without sufficient information about the more precise location of these changes. In classifying these cases, as usual, the occluded arteries are taken into consideration. In Case

[1] The studies here presented were carried out with the aid of a grant from P. Carl Petersen's Fond.

half» in 2 cases, »quite distally» in 1 case, »in its extreme part» in 1 case, and in 3 cases the site of the occlusion was not given. Finally, the left circumflex branch was occluded »above» in 1 case, »3 cm from the branching» in 1 case, »4 cm from the branching» in 2 cases, »6 cm from the branching» in 1 case, while in 1 case the site of the occlusion was not given.

It will be noticed that — just as in the groups of solitary infarcts — the pathologic-anatomical features were subject to very great variation.

*Electrocardiograms.* — Only 18 out of these 20 patients were examined by electrocardiography. A total of 122 electrocardiograms were taken, and they were all pathological. The more important electrocardiographic abnormalities are recorded in Table 1 after the same principles as adopted in Table 1 in the preceding paper.

*QRS Complex.* As is evident from Table 1, QRS changes of the anterior wall type were found only in 4 cases: a large $Q_1$ in every case, in 2 cases the $Q_1$ wave formed the beginning of W-formed $QRS_1$ in some of the tracings. 3 of the cases (Nos 22, 23 and 28) showed at the same time a small $R_1$, and 1 of the cases a large $S_2$ and $S_3$ (Winternitz' Type I).

On the other hand, QRS changes of the posterior wall type were found in 12 of the 18 electrocardiographed cases. Thus a large $Q_3$ was seen in 9 cases, although in some of the records the $Q_3$ wave was not followed by an $R_3$, but in such instances the $QRS_3$ complex fulfilled Durant's criteria. In 3 cases only the Durant $QRS_3$ was seen. In all the 12 cases with a large $Q_3$ or a Durant $QRS_3$ a $Q_2$ wave was present. W-formed $QRS_2$ was found in 2 cases, M-formed $QRS_2$ likewise in 2 cases. Among other QRS changes it has to be mentioned that Winternitz' Type II was not found in any case, and Winternitz' Type III was found only in 1 case.

*RS—T and T.* RS—T and/or T changes of the anterior wall type were found only in 1 case, although a fresh anterior wall infarct was present in 9 out of the 18 patients examined by electrocardiography (in one of these cases, however, this examination was not carried out in relation to the fresh infarct). RS—T and/or T changes of the posterior wall type were found in 11 cases, but only in 7 of these could the changes be ascribed to infarction, as in the remaining 4 cases the changes could also be explained as attributable

to marked preponderance of the left side (depression of RS—$T_1$ and elevation of RS—$T_3$).

*Precordial Leads.* Electrocardiograms were taken with precordial leads in 17 out of the 20 cases. In 8 of these the records showed QRS changes that have to be characterized as anterior wall changes. On the whole the changes here were less pronounced than in the group of solitary anterior wall infarction. Thus, a completely negative QRS complex in both precordial leads was found only in 1 case (No. 23).

In the parasternal lead alone, a completely negative QRS complex was found in 5 cases (Nos. 23, 25, 26, 27 and 32), while a strikingly large Q wave as compared to the following R wave was seen in 2 cases (Nos. 22, 39) and a Q wave of 2 mm, followed by a very small R wave was seen in 1 case (No. 24). Thus an initial negative deflection in the parasternal lead was recorded in 8 cases. In the apical lead these 8 cases presented the following changes: Totally negative QRS complex in 1 case (No. 23), large Q wave followed by a small R wave in 1 case (No. 22), a Q wave of 2 mm followed by a small R wave in 1 case (No. 24), an initial R wave $<$ 10 mm in 1 case (No. 25), and a normal QRS complex with a small Q wave in 4 cases (Nos. 26, 27, 32 and 39).

Thus, of 17 electrocardiographed patients, 8 showed signs of anterior wall infarction in the parasternal lead, and in 3 of the cases this diagnosis was supported by the findings in the apical lead (in the remaining 5 cases the changes recorded in the apical lead did not go against the probability of anterior wall infarction, but were of no positive significance to this diagnosis). Of the remaining 9 cases in the group of anterior wall + posterior wall infarction, 1 patient (No. 36) showed an initial $R_d < 2$ mm and an initial $R_s < 10$ mm, while 2 patients (Nos. 28 and 33) showed an initial $R_s < 10$ mm (Case 33 was an instance of left bundle branch block).

In judging of the significance of the QRS changes to the diagnosis of infarction, it has to be kept in mind that marked hypertrophy of the left side of the heart may give a totally negative QRS complex in the parasternal lead, and it may be difficult to exclude this possibility.

As to RS—T and T in the precordial lead, 3 cases (Nos. 23, 24, and 28) sowed changes of the anterior wall type, while 2 cases (Nos, 25 and 26) showed changes of the anterior and posterior wall type

and 2 cases (Nos. 31 and 38) changes of the posterior wall type. The remaining 10 cases presented unspecific changes in RS—T and/or T. Also in estimating the RS—T and T changes one has to keep in mind the changes produced by marked hypertrophy of the left side of the heart.

*Diagnostic Value of the Electrocardiograms.* The electrocardiograms taken in derivations from the extremities were stamped quite preponderantly by the posterior wall changes, and only 4 cases showed changes suggestive of anterior wall infarction. On employment of extremity leads alone, in 2 of the cases (27 and 38) the diagnosis would have been anterior wall infarction, in 2 of the cases (23 and 28) anterior wall + posterior wall infarction, in 10 cases (24—27 and 29—34) posterior wall infarction, while in 4 cases (35, 36, 37 and 39) the infarction could not be diagnosed electrocardiographically (although Case 37 would reasonably be suspected of anterior wall infarction — owing to disturbances in the conduction that will be mentioned later on).

On employment of extremity + precordial leads, the diagnosis would be anterior wall infarction in 2 cases (22, 39), anterior wall + posterior wall infarction in 8 cases (23—28, 32 and 38), posterior wall infarction in 5 cases (29, 30, 31, 33 and 34), while the infarction could not be diagnosed in 2 cases (35 and 36).

It has been mentioned before that the electrocardiographic diagnosis of anterior wall infarction by means of derivations from the extremities alone is impracticable in about onehalf of the cases, unless the infarct is fresh. If the anterior wall infarction is associated with infarction of the posterior wall, the diagnosis of the anterior wall infarct is rendered even more difficult, as the derivations from the extremities are dominated by the posterior wall infarction. The diagnosis of the anterior wall infarct is rendered possible in a good many cases by means of the precordial leads, but there still remains a rather considerable factor of uncertainty in the incidence of several infarcts.

## Rest of the Cases (Other Combinations and »Vague Descriptions»).

The cases in this group (Nos. 42—51) are recorded in Table 2 [1].

[1] The Record Numbers of these cases were: 468/41, 87/39, 532/36, 935/38, 472/36, 81/40, 438/40, 478/40, 334/40 and 35/40.

**1.**

*Posterior Wall Infarction.*

electrocardiograms taken. (+) means that the abnormality was present but due to infarction.

| Large $Q_1$ | W-formed $QRS_1$ | Winternitz I | Winternitz II | Winternitz III | M-formed $QRS_2$ | W-formed $QRS_2$ | $Q_2 \geqq 1$ mm | Large $Q_3$ | Durant $QRS_3$ | RS-$T_1$ elevation | RS-$T_1$ depression | RS-$T_2$ elevation | RS-$T_2$ depression | RS-$T_3$ elevation | RS-$T_3$ depression | Coronary $T_1$ | Coronary $T_2$ | Coronary $T_3$ | Fresh ant. wall inf. | Fibrous ant. wall inf. | Fresh post. wall inf. | Fibrous post. wall inf. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| + | + | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | + | + |
| + | + | + | ÷ | + | ÷ | + | + | ÷ | + | ÷ | (+) | ÷ | ÷ | (+) | ÷ | ÷ | ÷ | ÷ | + | ÷ | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ | ÷ | + | ÷ | ÷ | + | ÷ | ÷ | + | + | + | + | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | + | ÷ | (+) | ÷ | ÷ | + | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ | ÷ | + | ÷ | + | ÷ | ÷ | ÷ | ÷ | + | ÷ | + | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | + | ÷ | + | ÷ | ÷ | + | ÷ | ÷ | + | + | ÷ | + | + | ÷ |
| + | ÷ | ÷ | ÷ | ÷ | + | ÷ | + | + | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | ÷ | + | ÷ | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ | + | ÷ | (+) | ÷ | ÷ | (+) | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ | ÷ | ÷ | ÷ | + | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ | ÷ | + | + | ÷ | + | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ | ÷ | + | + | ÷ | + | ÷ | ÷ | ÷ | + | ÷ | + | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | ÷ | ÷ | (+) | ÷ | ÷ | + | ÷ | ÷ | + | + | vague | | | |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | + | + | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | vague | | | |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | (+) | ÷ | ÷ | ÷ | ÷ | + | ÷ | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | + |
| ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | (+) | ÷ | ÷ | ÷ | ÷ | (+) | ÷ | ÷ | ÷ | + | ÷ | ÷ | + |
| + | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | + | ÷ | + | ÷ |
| ÷ | ÷ | ÷ | ÷ | + | ÷ | ÷ | ÷ | ÷ | ÷ | ÷ | (+) | ÷ | ÷ | (+) | ÷ | ÷ | ÷ | ÷ | + | ÷ | ÷ | + |
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*Autopsy Findings.* — The localizatio[illegible] of the infarcts in general will be seen from Table 2. It may b[illegible] t in particular that in 2 cases (43 and 44) the infarct w[illegible] he rigl[illegible]e, respectively in the lateral wall and [illegible] wall, combined with f[illegible]sis in other [illegible]oca[illegible] in Case 43 the [illegible]atchy fib[illegible] t t[illegible] myocardium [illegible]ase 44 t[illegible] shc fibrosis in t[illegible] of th[illegible] as[illegible] lateral infar[illegible]mbina[illegible] r wall infareti[illegible]es a[illegible] bined with a[illegible]ior (51) infarcts [illegible]wl[illegible] posterior wal[illegible] group, all the[illegible] heart, but so[illegible]

In 3 cases [illegible] cases showed l[illegible] ter case[illegible] recent [illegible] a fresh [illegible] and in C[illegible] tions of t[illegible]

In 2 c[illegible] in 2 cases [illegible] branch an[illegible] descending [illegible] left circumf[illegible] (44 and 51) t[illegible] coronary arte[illegible] it merely says [illegible]ly sclerotic.

As to the an[illegible] was given in 4 cas[illegible] tion», »3 cm from th[illegible] In the right coronary a[illegible] »2 cm from the branchi[illegible] the middle and distal th[illegible] most distal part». In the le[illegible] beginning of the branch» and

*Autopsy Findings.* — The localization of the infarcts in general will be seen from Table 2. It may be pointed out in particular that in 2 cases (43 and 44) the infarct was located in the right ventricle, respectively in the lateral wall and the posterior wall, in both cases combined with fibrosis in other parts of the myocardium. Thus, in Case 43 there was a »patchy fibrous configuration throughout the myocardium», while, in Case 44 the myocardium showed »areas of fibrosis in the anterior part of the septum». In 4 cases there was a lateral infarct in various combinations with anterior and posterior wall infarction, and in 3 cases an infarct of the septum was combined with anterior or posterior wall infarction. Finally, in 1 case (51) infarcts were seen »everywhere, especially in the anterior wall, posterior wall and septum (towards the apex)». As in the preceding group, all the cases presented presumably multiple infarction of the heart, but some of the cases were not quite clear-cut.

In 3 cases (42, 46 and 49) only fibrosis was found, while the other cases showed both fresh and fibrous changes, and in Table 2 the latter cases are designated so that the first-mentioned infarct is the recent one. In Case 45, however, the anterior wall presented both a fresh infarct and a fibrous (and also a fibrous lateral infarct); and in Case 51 the record mentions merely fresh and older affections of the myocardium everywhere.

In 2 cases (42 and 46) all the three main arteries were occluded; in 2 cases (48 and 49) the occlusion involved the anterior descending branch and the right coronary artery; in 1 case (45) the anterior descending branch and the left circumflex branch; in 1 case (47) the left circumflex branch and the right coronary artery; in 2 cases (44 and 51) the right coronary artery was occluded, and the other coronary arteries markedly sclerotic; and in 2 cases (43 and 50) it merely says in the records that the coronary arteries were markedly sclerotic.

As to the anterior descending branch the site of the occlusion was given in 4 cases: »in the upper part», »just below the bifurcation», »3 cm from the branching», and »4 cm from the branching». In the right coronary artery the occlusion was recorded in 5 cases as: »2 cm from the branching», »3 cm from the branching», »between the middle and distal thirds», »in the peripheral part» and »in the most distal part». In the left circumflex branch in 2 cases: »in the beginning of the branch» and »in the tip». As in the aforemen-

## Table 2.

*Survey of the Total 51 Cases of the Present Material.*

| Case No. | Site of infarction. | Number of cases | No. of electrocardiogr. pts. | Large $Q_1$ | W-formed $QRS_1$ | Winternitz I | Winternitz II | Winternitz III | M-formed $QRS_2$ | W-formed $QRS_2$ | $Q_2 \geqq 1$ mm | Large $Q_3$ | Durant $QRS_3$ | $RS\text{-}T_1$ elevation | $RS\text{-}T_1$ depression | $RS\text{-}T_2$ elevation | $RS\text{-}T_2$ depression | $RS\text{-}T_3$ elevation | $RS\text{-}T_3$ depression | Coronary $T_1$ | Coronary $T_2$ | Coronary $T_3$ | QRS of ant. wall type | RS-T of ant. wall type | QRS of post. wall type | RS-T of post. wall type |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1—12 | Anterior wall ..... | 12 | 11 | 3 | 1 | 3 | 0 | 1 | 1 | 2 | 3 | 1 | 2 | 6 | 0 | 4 | 4 | 2 | 6 | 4 | 3 | 2 | 4 | 8 | 2 | 2 |
| 13—19 | Posterior wall ..... | 7 | 6 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 4 | 4 | 2 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 2 | 0 | 0 | 6 | 2 |
| 20—21 | Lateral wall ..... | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 22—41 | Anterior + posterior wall | 20 | 18 | 4 | 2 | 1 | 0 | 1 | 2 | 2 | 14 | 9 | 5 | 0 | 5 | 2 | 2 | 6 | 0 | 1 | 3 | 5 | 4 | 1 | 12 | 7 |
| 42 | Ant. + post. + lat. wall | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 43—44 | Post. wall of right ventricle + other parts of myocardium ..... | 2 | 2 | 2 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 |
| 45—46 | Ant. + lateral wall .... | 2 | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 47 | Lateral + post. wall. .. | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 48 | Post. wall + septum .. | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| 49 | Ant. wall + septum. .. | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 50 | Septum + ant. wall? .. | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 51 | »Everywhere», especially ant. and post. wall and septum ..... | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| Total | | 51 | 46 | 10 | 4 | 4 | 0 | 6 | 7 | 6 | 26 | 19 | 9 | 6 | 8 | 7 | 6 | 12 | 6 | 5 | 9 | 11 | 11 | 9 | 25 | 14 |

The figures in the columns give the number of cases showing the respective electrocardiographic abnormalities.
The instances which in Tables 1 and 2 are recorded as (+) are not included in this account.

tioned groups, the site of the occlusion in the individual arteries was most variable.

*Electrocardiograms.* — Altogether 95 electrocardiograms were taken in these cases, and all 10 patients were examined in this way. Information about the occurrence of the more important electrocardiographic changes is given in Table 2. As it is out of the question from the individual cases in this group to derive any inference about any type of electrocardiographic changes in the various combinations of infarction, the individual cases will not be described in detail.

Of the 6 cases (42, 44, 45, 46, 49 and 51) in which anterior wall infarction was ascertained with certainty, 2 (Nos. 42 and 44) showed QRS changes of the anterior wall type in derivations from the extremities (large $Q_1$ + small $R_1$ and large $Q_2$ in most of the records). A large $Q_1$ was further found in Case 43, in which a »diffuse fibrous configuration was seen throughout the myocardium», *i. e.*, probably also an anterior wall infarct. RS–T and/or T changes of the anterior wall type were not found in any case (a *fresh* anterior wall infarct was found only in one case).

Of these 7 cases with unquestionable or probable anterior wall infarction, 3 (Nos. 45, 49 and 51) showed a completely negative QRS complex in the parasternal lead; 2 (Nos. 42 and 43) showed an initial R wave < 10 mm in the apical lead; and 2 showed no QRS changes in the precordial leads. Unquestionable RS-T and/or T changes of the anterior wall type were not found, but 1 case (45) showed inversion of the T wave in both precordial leads. This case was the only one in which there was found a fresh anterior wall infarct. (But, inverted T in both precordial leads was found also in 2 other cases (47 and 48), with lateral + posterior wall infarction and posterior wall + septum infarction, respectively.)

While anterior wall infarction could be diagnosed in 3 of the 7 cases on the extremity leads alone, the diagnosis could be made in 6 of the 7 cases on the extremity leads + the precordial.

Of the 6 cases in which posterior wall infarction was ascertained with certainty (Nos. 42, 43, 44, 47, 48 and 51) 4 presented QRS changes of posterior wall type in extremity leads (Nos. 44, 47, 48 and 51). Still, in one of these cases (No. 44) the $Q_3$ wave was not sufficiently large to meet the criteria, but it was associated with

other and very typical posterior wall changes. RS—T and/or T changes of the posterior wall type were found in 3 of the cases (44, 48 and 51). — In the precordial leads, a small initial R wave in the apical lead was found in 2 cases (42 and 43), and a completely negative QRS complex was found in 1 case (51). These 3 cases were at the same time affected by anterior wall infarction. No other QRS changes were recorded. RS—T and/or T changes of the posterior wall type in precordial leads were found only in 1 case (44). From the cases in this group it is further seen that the diagnosis posterior wall infarction can be made on the extremity leads with a fair degree of certainty even when this condition is combined with some other infarct, and the precordial leads are of no additional value for the diagnosis of posterior wall infarction.

Of the above-mentioned 6 cases of posterior wall infarction, 2 (Nos. 43 and 44) had the posterior wall infarct in the *right* ventricle. In one of these (No. 43) there was no sign of posterior wall infarction in the extremity and precordial leads; in the other case (No. 44) the $Q_2$ and $Q_3$ did not fulfil the criteria, but the records showed typical RS—T changes and auriculoventricular block.

## Survey of the Electrocardiograms in the Material in General.

Table 2 gives a survey of the occurrence of the more important electrocardiographic abnormalities in all the electrocardiographed cases considered under one.

QRS changes of the anterior wall type were found in 11 cases (large $Q_1$ in 10 cases, W-formed $QRS_1$ in 4, Winternitz' Type I in 4). All presented an anterior wall infarct, solitary or combined with other forms.

RS—T and/or T changes of the anterior wall type were found in 9 cases, all with an anterior wall infarct, solitary or combined with other forms. (The changes in Case 20, lateral infarction, were probably also of the anterior wall type (positive coronary $T_3$), but not reckoned under this heading.)

QRS changes of posterior wall type (large $Q_3$ or Durant $QRS_3$) were found in 25 cases. Of these, 21 presented a posterior wall infarct, solitary or combined, while 2 showed an anterior wall infarct, 1 a lateral infarct, and 1 anterior + posterior wall infarction.

RS—T and/or T changes of the posterior wall type were found in 14 cases, 12 of which presented a posterior wall infarct, solitary or combined, while 2 showed an anterior wall infarct.

Of other electrocardiographic abnormalities, the following are to be mentioned.

Winternitz' Type II did not occur at all. Winternitz' Type III was found in 6 cases, 1 of which showed an anterior wall infarct, 1 a posterior wall infarct, and 4 a combined infarction.

M-formed $QRS_2$ was found in 7 cases: 1 with anterior wall infarct, 1 with posterior wall infarct, and 5 with combined infarcts. W-formed $QRS_2$ was found in 6 cases: 2 with anterior wall infarct, 1 with posterior wall infarct, and 3 with combined infarcts.

$Q_2 \geqq 1$ mm was found in 26 cases: 3 with anterior wall infarct, 4 with posterior wall infarct, 1 with lateral infarct, and 18 with combined infarcts.

Further, the relatively rare occurrence of coronary T waves is to be pointed out. It is due to the fact that many of the infarcts were fibrous; and, as mentioned previously, the coronary T wave is no permanent change.

*Precordial Leads:* Initial negative deflection in both precordial leads was found in 9 cases (this category comprises also normal Q waves in the apical lead if the parasternal lead showed an abnormal initial negative deflection); 4 of these cases presented an anterior wall infarct, 3 showed anterior + posterior wall infarction, 1 anterior wall + septal infarction, and 1 lateral infarction.

Initial negative deflection in the parasternal lead alone was found in 7 cases: 5 with anterior + posterior wall infarcts, 1 with anterior wall + lateral infarction, and 1 with infarction of the anterior wall, posterior wall and lower part of the septum.

Initial negative deflection in the apical lead alone was not observed (apart from small normal Q waves).

Small initial R wave in both precordial leads was found in 3 cases: 1 with anterior + posterior wall infarction, and 2 with posterior wall infarcts.

Small initial R wave in the parasternal lead alone was found in 3 cases: 2 with anterior wall infarct, 1 with septal infarct (+ anterior wall infarct?) and, at the same time, marked preponderance of the left side.

Small initial R wave in Lead *s* alone was found in 7 cases: 2 with anterior wall infarct, 1 with posterior wall infarct, 3 with anterior + posterior wall infarction (1 of these with left bundle branch block at the same time), and 1 with anterior-posterior wall + lateral infarction.

As to RS—T and T in the precordial leads, the following data are to be mentioned: Elevation of RS—T in both precordial leads was found in 10 cases: 8 with anterior wall infarct, 2 with anterior + posterior wall infarction. Depression of RS—T in both precordial leads was found in 6 cases: 1 with posterior wall infarct, 5 with combined posterior wall infarction.

Inversion of the T wave in Lead *d* alone was found only in 1 case, in Lead *s* alone in 17 cases, and in both precordial leads in 13. Presumably the T changes were influenced strongly by the hypertrophy of the left side of the heart (as is indicated by the frequent occurrence of an isolated T inversion in Lead *s*). Of the cases with inverted T in both precordial leads, 3 showed a clear-cut anterior wall infarct, 5 had anterior + posterior wall infarction, 1 had infarction of the septum and probably of the anterior wall, too, 1 had a lateral infarction, 1 had lateral + posterior wall infarction. 1 had posterior wall infarct, and 1 infarction of the posterior wall + septum. So inversion of the wave in both precordial leads, which is a very common phenomenon in anterior wall infarction in the subacute stage (in this material several patients died with infarction of the anterior wall alone so early that this electrocardiographic abnormality could not be expected to appear), may thus be seen also in lateral infarction, in posterior wall infarction and in various combinations.

Isolated inversion of the T wave in Lead *s* was not found to be associated in particular with any certain type of infarction and it is probably to be attributed to marked hypertrophy of the left side of the heart.

Even though the precordial leads proved of considerable value in this material, too, they did not show such characteristic changes in anterior wall infarction as revealed by Leads $CF_2$ and IVF in a material of anterior wall infarcts reported previously, and this fact asserts itself even if we limit this consideration to the group of solitary anterior wall infarcts alone. Nevertheless, this difference might be explained as attributable to differences in the

two materials, and it is not practicable from the present basis to estimate which precordial leads are the more suitable for the diagnosis anterior wall infarction. This question can be answered satisfactorily only through examination of a number of cases with simultaneous registration of the precordial leads with the indifferent electrode placed respectively on the right arm and left leg. Such studies have been commenced and the preliminary findings suggest that derivations with the indifferent electrode placed on the left leg offer some advantage to derivations with the indifferent electrode on the right arm. If this be confirmed, it means a strong plus in favor of the employment of the indifferent electrode on the left leg as a routine derivation, since it is primarily in anterior wall infarction that precordial leads are particularly serviceable.

*Disturbances of Conduction and Arrhythmia.* — Of the 46 electrocardiograph patients, 23 showed signs of defective conduction and arrhythmia.

Prolonged auriculoventricular conduction was found in 4 cases (*13*, 25, *31* and 48). They all had posterior wall infarction, alone or combined, and in all 4 cases the posterior wall infarct was fresh. Auriculoventricular block was found in 2 cases (37 and 44), both with combined posterior wall infarction.

Auricular fibrillation was found in 4 cases (*7*, *11*, *31* and 43): 2 with anterior wall infarct, 1 with anterior + posterior wall infarct, and 1 with infarction of the posterior wall of the right ventricle besides »patchy, fibrous configuration throughout».

Extrasystoles were found in 12 cases, distributed evenly on the various groups.

Ventricular paroxysmal tachycardia was found in 4 cases: 3 with anterior wall infarct (*2*, *7* and *9*), 1 with anterior + posterior wall infarction (*23*).

Left bundle branch block (new nomenclature) was found in 5 cases: 3 with anterior wall infarct (2, 4 and 5), 2 with anterior + posterior wall infarction (33 and *37*).

Wilson block (right bundle branch block with a large, wide $S_1$) was found in 2 cases: 1 with anterior wall infarct (7), and 1 with anterior + posterior wall infarction (*37*).

As will be noticed, several cases showed various forms of disturbances in conduction or arrythmia; in many of these cases (the ones reported in italics), these phenomena were transitory.

## On the Electrocardiographic Diagnosis of Cardiac Infarction.

From the above it is evident that, in dealing with an autopsy material, the electrocardiographic changes in cardiac infarction do not meet the requirements as to definition and consistency that we are inclined to set up in keeping with many clinical works. As mentioned in the introduction, the explanation of this is to be looked for chiefly in the circumstance that the types of electrocardiographic changes described by the clinical writers in some degree are based upon the supposition that the underlying infarct has a typical location in an otherwise well-preserved myocardium, whereas the autopsy material shows the pathologic-anatomical findings to be exceedingly polymorphous — not only because of the frequent occurrence of multiple infarcts in various combinations, but also within the groups of solitary infarcts. Undoubtedly there is a tendency to overestimate the connection between cardiac infarction and various electrocardiographic changes, so that the diagnosis cardiac infarction is considered improbable, or even ruled out, if certain changes fail to appear in the electrocardiograms. As a matter of fact, however, various electrocardiographic changes make their appearance preferably in certain types of cardiac infarction, being thus of great diagnostic significance but these electrocardiographic abnormalities are found only in a part of the cases of cardiac infarction, and hence their absence cannot be of any particular significance to the exclusion of cardiac infarction.

It is to be kept in mind that in the clinic the diagnosis cardiac infarction is made largely by means of electrocardiography — the topographical diagnosis almost exclusively in this way. Several of the cases in which no typical electrocardiographic changes are recorded — and this applies in particular to the chronic cases — are not diagnosed. A clinical material of cardiac infarcts may therefore readily give some exaggerated ideas about the regularity of the electrocardiographic changes.

Various circumstances contribute in particular to the eventual failure of the electrocardiographic diagnosis of cardiac infarction: The best known and most constant changes, the changes in RS—T and T, belong to the acute and subacute stages of the lesion (and

this applies to the coronary T, too). If the infarct is more than a few months old the RS—T and T changes will often have lost the features characteristic of infarction. This applies especially to anterior wall infarction, in which the later changes, negative $T_1$ and positive $T_3$, readily may be mistaken for the changes commonly seen in preponderance of the left side.

The QRS changes, on the other hand, are more permanent, but a previous material as well as the present show that these changes fail to appear even in about one-half of the clear-cut cases of anterior wall infarction. If the anterior wall infarct is combined with posterior wall infarction, the typical QRS changes fail to appear even more often. If we are not dealing with acute infarction, which in most instances can be diagnosed by sufficiently frequent electrocardiography and comparison of the electrocardiograms taken, the electrocardiographic diagnosis of cardiac infarction by means of derivations from the extremities falls short in many respects; in particular, the diagnosis of multiple infarcts is most uncertain.

As shown in the preceding, on employment of precordial leads as a supplement to derivations from the extremities, the diagnosis is improved quite considerably — because the precordial leads in particular make it possible to diagnose the anterior wall infarct, the type of infarction in which the extremity leads most often fail.

Possibly the present material comprises particularly many complicated cases and thus shows less schematic electrocardiographic changes than are generally encountered in materials of cardiac infarction. This department of the Rigshospital receives also municipal patients, it is true, and thus — besides through admission of private patients — several patients are admitted with recent infarction from first-time occlusion, but the majority of its patients come from the provinces. The latter patients do not enter this hospital during their first attack of coronary occlusion, but at a later point of time — after the second occlusion, or perhaps after the third — after the development of a severe chronic cardiac insufficiency that is amenable to treatment but slightly. More likely, then, the material from a municipal hospital would show more clear-cut electrocardiographic changes, as a greater part of the material would be made up of recent cases of first-time occlusion.

Even though acute coronary occlusion has a high primary mortality, the autopsy material presented here shows that not a

few patients survive their first attack of coronary occlusion, only to succumb after the second or third attack. Thus, chronic cardiac infarction is no rare affection, and it may be of considerable prognostic significance, from the large group of arteriosclerotic heart lesions, to pick out these cases for analysis. Electrocardiography is our principal adjuvant in this task, but it is necessary to supplement the extremity leads with precordial leads if not too many cases are to remain undiagnosed.

## Summary.

An autopsy material of 51 cases of acute and fibrous cardiac infarction is presented for elucidation of the relation between the electrocardiograms and the autopsy findings.

The pathologic-anatomical changes were highly polymorphous: a single infarct was found only in 21 cases, while the remaining cases showed several coexisting infarcts in various combinations.

Electrocardiograms were taken in 46 of these cases — altogether 419 electrocardiograms.

Of the 46 cases, 9 (*i. e.*, about 20 %) showed no electrocardiographic changes in the extremity leads, while 5 out of 45 cases (*i. e.*, about 11 %) showed no electrocardiographic sign of cardiac infarction in any of the derivations (from the extremities as well as precordial).

Out of 11 cases of solitary anterior wall infarcts, only 6 showed evidence of anterior wall infarction in the extremity leads, and 2 showed signs of posterior wall infarction. On employment of extremity + precordial leads, signs of anterior wall infarction were found in 9 of the 11 cases.

Among 6 cases of solitary posterior wall infarct, 3 showed pronounced signs of posterior wall infarction in the extremity leads, and 3 showed less pronounced signs of posterior wall infarction. Here the precordial leads were of no additional diagnostic value.

In 18 cases of anterior + posterior wall infarction only 4 showed signs of anterior wall infarction in the extremity leads. On employment of extremity + precordial leads, signs of anterior wall infarction were found in 10 out of 17 cases. Of the 18 cases of anterior + posterior wall infarction, 12 showed signs of posterior wall infarction in the extremity leads. On employment of extre-

mity + precordial leads, signs of posterior wall infarction were found in 13 out of 17 cases.

Among 7 cases of anterior wall infarction in other combinations, 3 showed signs of anterior wall infarction in the extremity leads. On employment of extremity + precordial leads, signs of anterior wall infarction were found in 6 of the 7 cases.

Of 6 cases of posterior wall infarction in other combinations, 4 showed signs of posterior wall infarction in the extremity leads. Precordial leads were of no additional diagnostic value in these cases.

Thus, anterior wall infarction, clear-cut or combined, was found in 36 cases. Only 13 of these (*i. e.*, about 36 %) showed signs of anterior wall infarction in the extremity leads, whereas employment of extremity + precordial leads gave signs of anterior wall infarction in 25 out of 35 cases (*i. e.*, about 71 %).

Posterior wall infarction, solitary or combined was found in 30 cases, 22 of which (*i. e.*, about 73 %) showed signs of posterior wall infarction in the extremity leads. On employment of extremity + precordial leads, signs of posterior wall infarction were found in 23 out of 29 cases (*i. e.*, about 79 %).

On employment of the extremity leads alone, the diagnosis of anterior wall infarction failed in about one-half of the cases when the infarct was solitary, and in about three-fourths of the cases when the infarct was combined with posterior wall infarction. On employment of extremity + precordial leads, the electrocardiographic diagnosis of anterior wall infarction improved considerably, but it still remained uncertain in the combination of anterior + posterior wall infarction.

Further studies will aim to settle whether employment of precordial leads with the indifferent electrode on the left leg will mean an additional improvement of the diagnosis of anterior wall infarction, as preliminary experiences are suggestive of this.

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A more comprehensive list of the more recent works on electrocardiographic changes in cardiac infarction is given in the bibliography of No. 7.

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# Postural Hypotension in a Patient with Multiple Encephalomalacias.

By

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(Submitted for publication April 9, 1942).

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Vasoconstriction in the splanchnic area is considered to be the most important factor counteracting a lowering of the blood pressure in an upright position. The sympathetic vascular reflex arising upon changing the recumbent position to a standing posture is released by pressorsensitive receptors in the walls of the periferal vessels (1, 2, 3, 4). The receptors most studied are those in the carotid sinuses and in the aorta. Receptors in the splanchnic and thoracic vessels appear to be of special importance for the orthostatic regulation of the blood pressure.

The vasomotor and cardio-regulatory reflexes have medullary and hypothalamic centres. The existence of the medullary centres is known from Hill's fundamental works on the influence of the force of gravity on the circulation of the blood. The importance of the hypothalamus was demonstrated by Barbour 1912, Karpus and Kreidl 1918 and has in the last years been studied by Bronk, Cushing, Beattie and others (9).

Elevated as well as low blood pressures are reported in cases of tumors in various parts of the hypothalamus (10). We have found no data on orthostatic disturbances in cerebral affections.

Already Addison observed such symtoms in cases of suprarenal insufficiency (13). Cannon and Heymans and Ladon have shown that a fall in blood pressure produces an increased secretion of epinephrine, which, trough both humoral and reflectory mechanisms, regulates vascular tone, cardiac rate and circulating blood volume (11, 12).

Upon changing from a recumbent to an erect posture, there appears in man, under physiological conditions, a slight decrease in the systolic and a slight increase in the diastolic blood pressure and an acceleration of the pulse averaging about 20 beats a minute. In pronounced orthostatic drop in the blood pressure the acceleration of the pulse parallels the fall in blood pressure, if the cardio-accelerator reflex is unimpaired.

The most common type of orthostatic fall in blood pressure is the one appearing in the so called arterial orthostatic anemia. This syndrome, described and interpreted by Laurell, Bjure and Åkesson, is a constitutional anomaly, appearing especially in young people and children of an asthenic body build (14—17). It is frequently combined with visceral ptosis. In arterial orthostatic anemia there occurs, in upright position, a compensatory quickening of the pulse averaging about 40 beats a minute.

In 1925 Bradbury and Egglestone described the first cases of postural hypotension (18). This syndrome is characterized by a marked fall in blood pressure in a standing posture without any compensatory quickening of the pulse. In addition to the symtoms caused by this circulatory insufficiency in erect position, there occurs divers other disturbances as anhidrosis, which is not resistant to pilocarpine, reflex disturbances e. g. Addie's syndrome, low basal metabolic rate, impotence and intestinal disturbances (18—34). Bradbury and Egglestone described the syndrome as »an extensive and peculiar disturbance in the functional activity of the vegetative nervous system».

The cases described as postural hypotension with tachycardia (Sanders, Baker and Hughes and Yusaf) present a picture in complete agreement with that of arterial orthostatic anemia (35—37). It is necessary to distinguish between arterial orthostatic anemia and postural hypotension, two syndromes of different origin.

A third type of orthostatic fall in blood pressure, different from both types mentioned above, is described after extensive sympathectomies in hypertension (Roth and Hammarström) [1].

## Case report.

H. A. J. Associated Judge of Appeal, age 48. S:t Erik's Hosp. No. 2111/1941.

*Previous history:* as a child detachment of the retina of the right eye, wich has since been amaurotic. Otherwise well until the autumn of 1934, when the patient began to suffer from slight attacks of dizziness and buzzing in the ears. *One morning in the spring of 1935 the patient very suddenly felt unwell, started vomiting and felt dizzy as soon as he endeavoured to rise.* One the same day he was admitted to the Ear Dept. of Malmö Gen. Hosp. On examination nystagmus, Romberg vacillating. Babinski positive on the left side. Well and discharged from hospital after a week.

Felt well until 1937, when he began to experience slight temporary attacks of dizziness. For several years his skin had been strikingly dry. No perspiration on hot summer days. Difficult to perspire in Turkish bath.

In the night of Aug. 12, 1938, severe dizziness and persistent vomiting. Again admitted to Malmö Gen. Hosp. After the attack fumblingness and adiadochokinesia in the right arm and slurred speech. Walk, unsteady. On pointing deviation towards the left with the left arm.

Admitted to the Neurosurgical Dept. of Prof. Olivecrona in the Serafimer Hospital twice, in Sept. and Oct. 1938. Encephalograms showed slightly widened lateral ventricles and widened sulci on the convexity Otherwise normal conditions. The blood pressure varied between 190/120 and 160/110 mm Hg. Nothing to indicate the presence of an intracranial expansive process. Increasing mental blunting ever since 1938. Slightly euphoric state of mind. Loss of memory. Impaired ability to learn.

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[1] The most pronounced fall of blood pressure of this type is observed after Smithwich's operation, the extent of the fall of pressure being dependent on the extent of the denervation of the *splanchnic* area. Roth has found the ortostatic conditions to be normal after various sympathectomies involving the extirpation of minor parts of the lumbar or cervical chain of the sympathetic ganglia. One of us (Hammarström) had the opportunity of studying one of Docent O. Sjöquist's patients, who had been subjected to *repeated sympathectomies without the splanchnic roots being removed.* The case is a young man of 18, who since the age of eight suffered from severe pains in the limbs combined with paroxysmal increases in the blood pressure.

Repeated explorations disclosed no pheochromocytoma. To eliminate the pains in the limbs bilateral extirpations of the sympathetic chain of ganglia from L IV up to and including L II have been carried out, as well as bilateral extirpations of the ganglion stellatum and the middle cervical, all so far with good effect. In one of the explorations the ganglion coeliacum was also extirpated. Orthostatic tests on the tilting table proved the patient's blood pressure and pulse to be normal after these operations. In a lying position the blood pressure was 135/100 mm Hg and the frequency of the pulse 68 beats a minute and after 10 minutes in a standing position the blood pressure and pulse were 135/105 and 88 respectively.

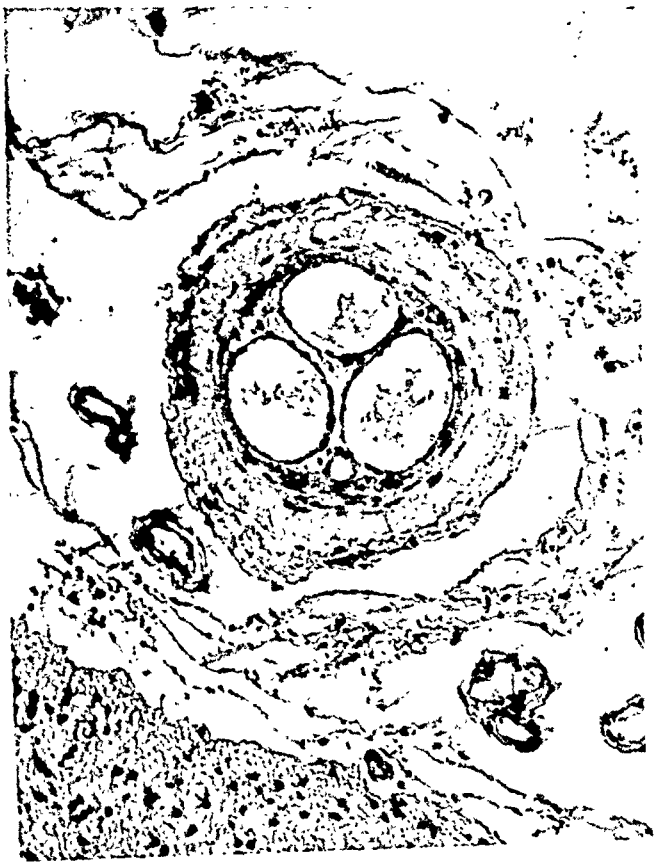


Fig. 1. Prep. 5. Recanaliced embolus in pial artery. v. Gieson. 140 x.

In April 1939 sudden weakness in the right leg. Could not use the leg for an hour, later it felt weak and flaccid. Consulted Prof. Hilding Bergfor the first time on April 13, 1939: Blood pressure 180/120. Cor: Slight enlargement to the left. Regular rhythm. Systolic murmur with maximum at the apex. The urine contained albumen but no pathologic sediment. Nonprotein nitrogen: 49.2 mg %. Creatinic clearence according to Rehberg 90 $cm^3$/min.

Since December 1940 worse. The patient was compelled to discontinue his work, which he had so far been able to attend to, his wife acting as his assistant and secretary. Scanning of speach increasing. Failing vision, unable to read. Severe fatigue. No dyspnoea on ordinary movements. No oedema. *Since the beginning of April 1941 the patient has fainted on a couple of occasions when sitting up or getting out of bed.* The patient then tumbled over, grew pale and faint but did not become completely unconscius. As soon as the patient resumed a horizontal position, he rapidly recovered.

Admitted to the Hospital on April 24, 1941.

*Physical Examination:* Of sturdy body build. Skin cool and dry, not peeling. Slight moisture in the axillae. Hands and feet cyanotic. No cyanosis of the lips. No oedema.

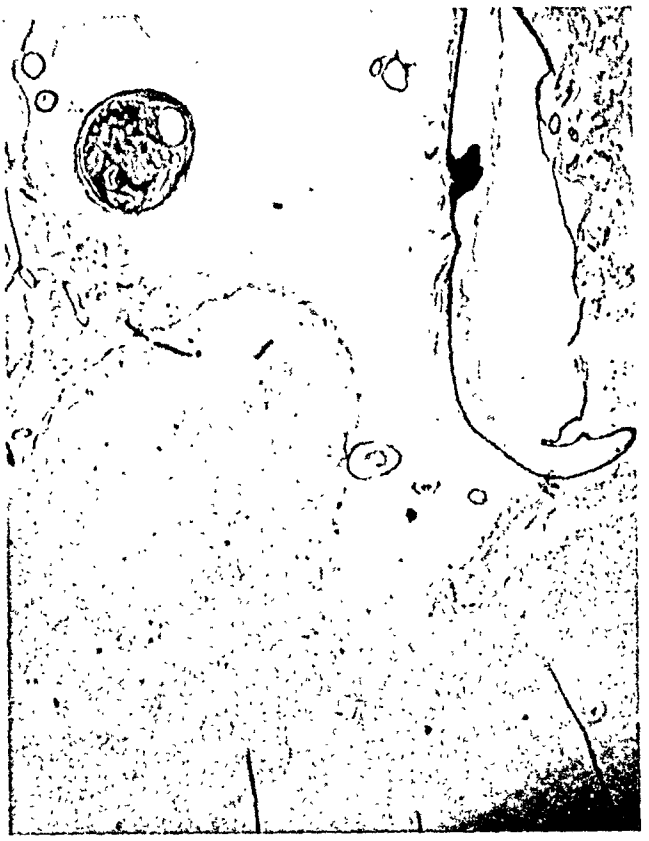
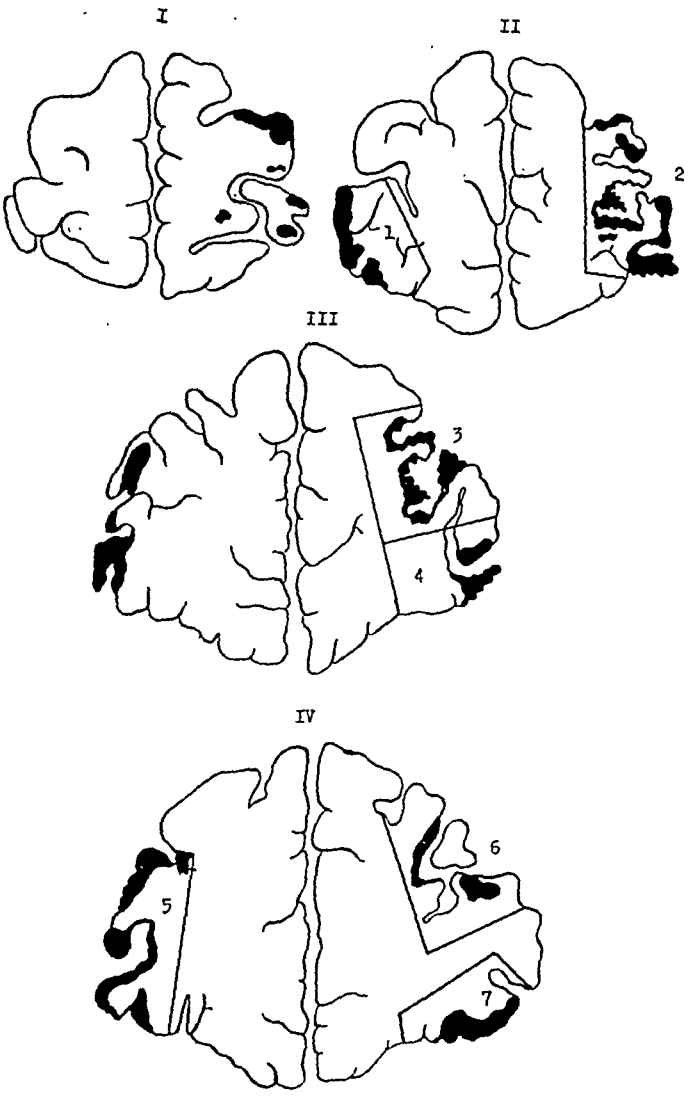


Fig. 2. Prep. 38. Recanaliced embolus in pial artery with laminary malacia. v. Gieson. 15 x.

Cor.: Left border just outside the mamillary line, 13 cm from the midline. Regular rhythm. Systolic murmur with maximum at the apex. P: II accentuated. Blood pressure 210/130 in recumbent position. Examination of the mouth, throat, abdomen, and lungs disclosed no pathologic conditions.

*Eye examination:* The right eye amaurotic. The fundus cannot be inspected owing to lens opacities. The left eye: Quantitative lightperception with poor localization. Fundus shows blurring of the margin of the disk. The arteries show distinct variations in lumen and typical sclerotic arteriovenous crossings. Slight haemorrhages and white exudates along the vessels.

*Central nervous system.* (Dr. R. Bringel): Mental condition: Emotionally labile. Emotional responses not always adequate. Some difficulties in perception. Somewhat slow mental reaction. Perseveration sometimes marked. Moderate amnesia for words. Apraxia; only very coarse coordination movements possible. No marked pareses. Considerably increased tone, whithout cog-wheel phenomenon, especially in the right arm and hand. Muscular reflexes generally and excessively increased. Foot clonus, spinal autonomous reflexes, Babinski and Rossolimo positive bilaterally. Superficial and deep sensibility practically intact. Hyperesthesia to pin

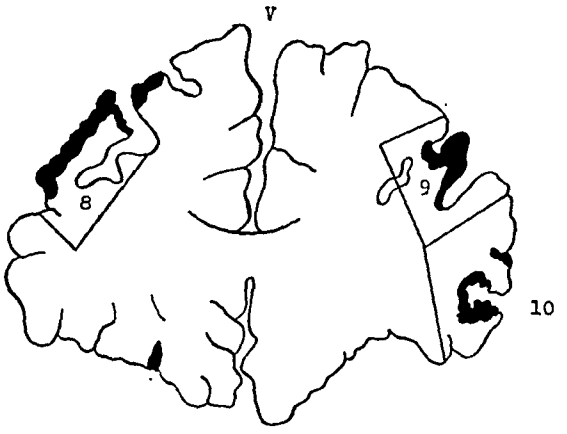


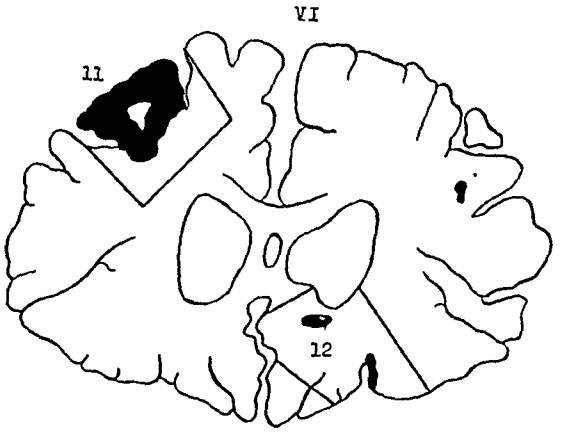

point in various areas. Cranial nerves: No facial paresis, no lingual or palatal paresis. General catalepsy. Test phrases slurred without typical errors. Pupillary light reflex slow on the left and barely noticeable on the right. Summary: Numerous symptoms of disseminated lesions in the central nervous system.

*Examination of orthostatic reaction:* Repeated examinations on the tilting table showed on changing from recumbent to erect position immediate fall in blood pressure with the patient fainting after 2 to 4 minutes.

A tight bandage around the waist did not prevent the orthostatic fall in blood pressure.

The respiration registered with the aid of a Krogh apparatus showed no change in depth or frequency during the orthostatic blood pressure fall.




| May 3, 1941. | Blood pressure | Pulse Beats/min. |
|---|---|---|
| Recumbent for 10 min. | 210/140 | 80 |
| Erect » ½ » | 90/80 | 96 |
| » » 1 » | 90/80 | 96 |
| » » 2 » | Fainted | |
| Recumbent » 2 » | 200/130 | 80 |
| Tilting the table to an angle of 45°: | | |
| 1 min. | 170/125 | 96 |
| 5 » | 145/115 | 100 |
| 9 » | 125/90 | 96 |
| 10 » | Fainted | |
| Horizontal position: | | |
| 1 min. | 190/130 | 96 |

Electrocardiogram in recumbent position — blood pressure 200/130. Sinus rhythm 80 beats a min. P — Q 0.14 sec. No axis deviation. T: 1 slightly positive, T: 3 slightly negative. Lead 4 normal.

Electrocardiogram in erect position — blood pressure 90/80. Sinus rhythm 98 beats a minute. Slight right preponderence. T: 1 more positive, T: 2 and T: 3 distinctly negative.

| Prep. Nr | c o r t e x | | | | | | Medulla | Leptomeninges | | Age of malacia |
|---|---|---|---|---|---|---|---|---|---|---|
| | Recent thrombus | Older thrombus without recanalisation | Old thrombus with recanalisation | Lammary malacias | Glious scars | Granular atrophy | Malacias in the white matter | Lipoid makrophags | Roundcells | |
| 1 | + | + | — | + | + | + | — | (+) | (+) | 2 weeks |
| 2 | — | — | ++ | (+) | + | ++ | + | — | — | years |
| 3 | — | + | (+) | ++ | ++ | ++ | + | — | — | 1 month |
| 4 | — | + | + | ++ | ++ | + | + | + | + | 1 month |
| 5 | — | + | ++ | ++ | ++ | ++ | + | + | + | 2—3 months |
| 6 | — | + | + | + | + | ++ | + | (+) | (+) | 2 months |
| 7 | — | + | — | + | + | + | (+) | (+) | (+) | 3 weeks |
| 8 | — | + | + | ++ | + | + | ++ | (+) | (+) | 2 months |
| 9 | + | ++ | + | ++ | ++ | ++ | ++ | (+) | (+) | years + 2 ws |
| 10 | — | + | — | ++ | + | + | (+) | — | — | 2—3 months |
| 11 | — | — | + | + | (+) | ++ | (+) | — | (+) | years |
| 12 | — | + | — | (+) | ++ | (+) | ++ | — | — | 2—3 months |
| 13 | — | — | ++ | ++ | ++ | — | + | — | — | years |
| 14 | — | — | + | (+) | ++ | — | (+) | — | — | years |
| 15 | — | + | — | — | + | — | — | — | — | 3—4 months |
| 16 | — | + | (+) | — | + | — | (+) | — | — | years |
| 17 | — | — | + | + | ++ | ++ | + | (+) | (+) | years |
| 18 | — | — | + | + | + | — | + | — | — | years |
| 19 | — | — | + | — | + | — | + | — | — | years |
| 20 | — | + | + | + | + | + | (+) | — | — | years |
| 21 | — | — | + | — | + | — | + | — | — | years |
| 22 | — | — | ++ | ++ | ++ | ++ | + | — | — | years |
| 23 | — | — | ++ | (+) | ++ | — | + | — | — | ys + 2—3 ws |
| 24 | + | + | + | + | + | ++ | + | + | + | ys + 1 w |
| 25 | + | — | + | ++ | ++ | (+) | + | — | (+) | 1 year |
| 26 | — | — | + | — | + | — | + | — | — | 1—2 weeks |
| 27 | + | + | — | + | + | ++ | (+) | + | + | 1 week |
| 28 | ++ | — | — | ++ | (+) | — | + | + | + | 1—2 weeks |
| 29 | + | + | — | (+) | ++ | (+) | (+) | + | (+) | 2—3 months |
| 30 | — | + | — | + | + | + | — | — | — | ys + 2 ws |
| 31 | ++ | — | (+) | ++ | ++ | ++ | ++ | + | ++ | years |
| 32 | — | — | + | — | + | — | — | — | — | 2—3 months |
| 33 | — | ++ | — | + | + | (+) | + | (+) | + | 3—4 months |
| 34 | — | ++ | + | ++ | + | + | + | — | — | 2—3 weeks |
| 35 | + | + | — | ++ | + | — | + | (+) | ++ | 3—4 weeks |
| 36 | + | ++ | — | + | + | (+) | + | — | + | 3—4 weeks |
| 37 | — | + | + | + | + | + | + | (+) | + | 3—4 months |
| 38 | — | — | ++ | + | + | + | + | — | + | years |
| 39 | — | — | ++ | ++ | + | + | + | — | — | years |
| 40 | — | — | ++ | + | ++ | (+) | + | — | — | 3—4 months |
| 41 | — | + | + | + | + | + | + | + | ++ | 1—2 months |
| 42 | — | + | + | + | + | + | + | + | ++ | 3—4 months |
| 43 | — | + | + | + | + | + | + | (+) | + | years |
| 44 | — | — | + | — | + | — | ++ | — | (+) | |

The orthostatic electrocardiographic changes are within normal limits.

The blood pressure was measured every two hours during 24 hours while the patient was in bed and showed systolic variations between 220 and 180 and diastolic between 140 and 130, mean 198/134 mm Hg.

Amytal test — 0.20 g isoamylaetylmalonylcarbamide 4 times with one hour's interval — showed a fall o f blood pressure from 210/145 to 180/120. Sodium nitrite test — 0.032 g six times with a half-hour's interval — fall of blood pressure from 175/110 to 145/100.

Immersion of one hand in water of + 4° C (according to Hines) caused an increase in the blood pressure from 220/130 to 245/140 in half a minute.

*Laboratory tests:* Red blood-cells 4.04 millions. Hgbl 80 %. White blood-cells 9.200. Urine: Sp. g. 1.016—1.025. Trace of albumen. Sediment showed nothing pathological. Basal metabolic rate — 6 %. Creatinine clearence according to Rehberg gave a filtration of 83.6 $cm^3$/min. Non-protein nitrogen on May 5th 52 mg %, on May 20th 89 mg %. Kahn negative. Sedimentation rate on Apr. 25th 39—62 mm in 1—2 hrs, on May 6th 74—108 mm, on May 12th 71—99 mm.

During the patient's stay in hospital, his condition rapidly changed for the worse; he fainted several times and tumbled over upon trying to get out of bed. Recovered immediately upon being put to bed. Persistent constipation. Temperature subfebrile between 36.9 and 38° up to May 19th, when the temperature rose rapidly. Died on May 21st in terminal pneumonia.

## Autopsy report. (St. Erik O. 212/41)

Weight of heart 440 g, slight hypertrophy of the left ventricle but no marked dilatation.

Endocardium: The mitral orifice of normal width, the sails slightly thickened, on the ventricular side covered with cauli-flower-like granulations not easily removed. The semilunar valves of the aorta are within a short space adherent and show signs of a recent verrucous endocarditis. No thrombi in the auricles.

Myocardium greyish brown. Numerous partly scattered, partly confluent old, small scars in the left ventricle and at the apex a scar of 3 cm diameter.

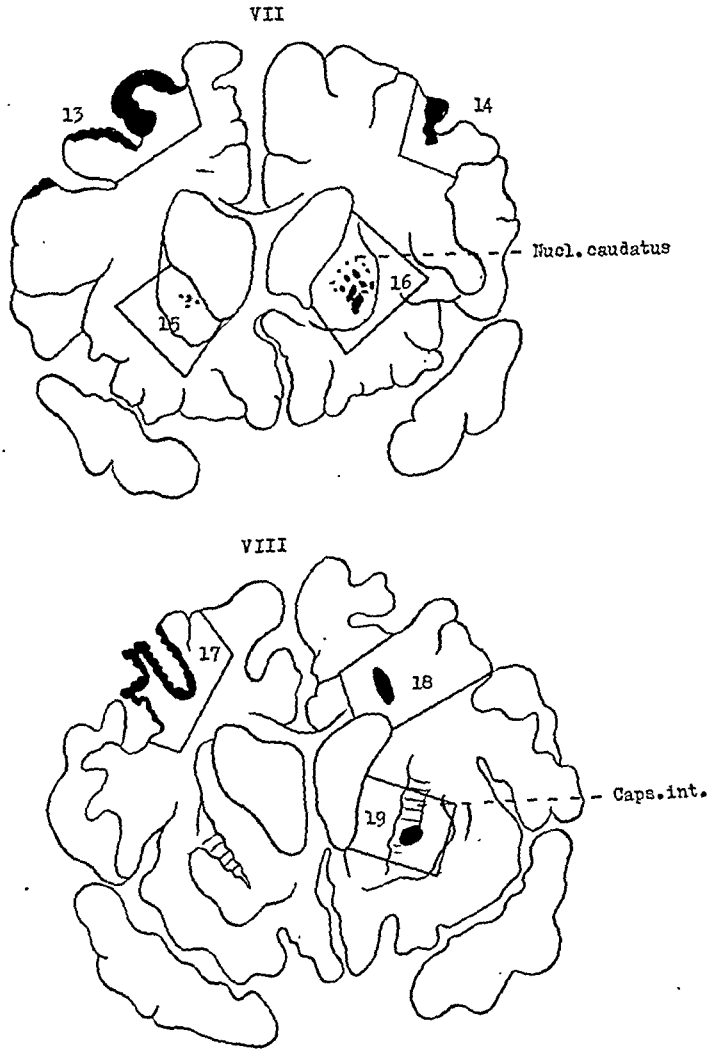
The coronary arteries show only slight arteriosclerotic changes.

The aorta shows fairly marked arteriosclerosis, considering the age of the man, of a thickend, hypertrophic rather than of an ulcerative type in the thoracic part.

Pleurae: On the left side loose adhesions at the top, the right side normal. Lungs large, heavy, rich in blood, partly fixed by injection of formaldehyde into the carotid arteries before the autopsy.

Peritoneal cavity normal. Intestines normal. Weight of spleen 190 g; it shows slight congestion and an old infarct the size of a hazelnut.

Suprarenals normal. Total weight of the kidneys 275 g; The cortex is narrow, the surface shows fine granulation. The renal pelvices and ureters normal. The pelvic organs show no pathologic changes.




Weight of the thyroid 30 g, normal. Oesophagus, stomach and pancreas normal. Bile ducts patent. Liver of normal size, rich in blood, normal.

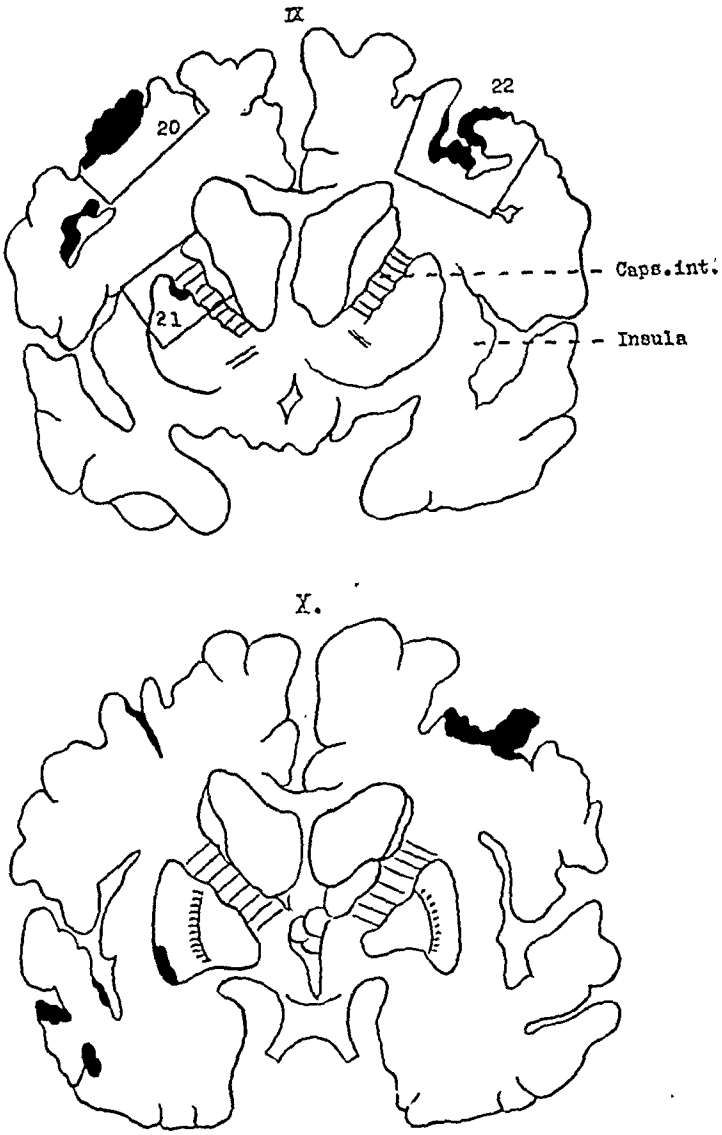
The *brain* was fixed *in situ* by injecting a 10 % solution of formaldehyde into the carotid arteries. The basal arteries show no arteriosclerosis.

*Pons and medulla oblongata normal.*

*Cerebellum.* On the right side, mainly in the white but also in the adjoining grey substance there is an old encephalomalacia of irregular shape and the size of two white beans.

*Cerebrum.* Eighteen frontal sections were made through the cerebrum. Each section is found to contain about four large or small encephalomalacias of a type similar to that in the cerebellum. Judging by their macroscopic appearence, most of the malacias may be a year or more old, but some appear, to be of a more recent date.

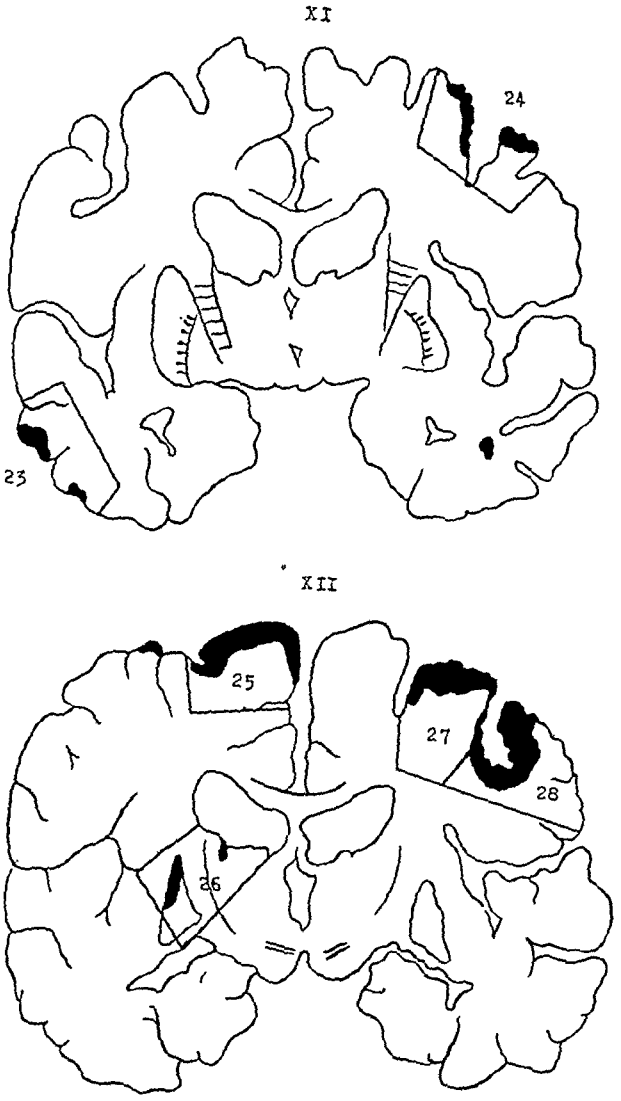
The great majority of these malacias are localized to various parts of the cortex, occasionally being found in but certain layers of the cortex. A




striking fact is that the affected parts of the cortex are very much narrower than the adjoining normal parts and display a peculiar notched appearance, a microgyria. The colour of the malacias is generally slightly brownish.

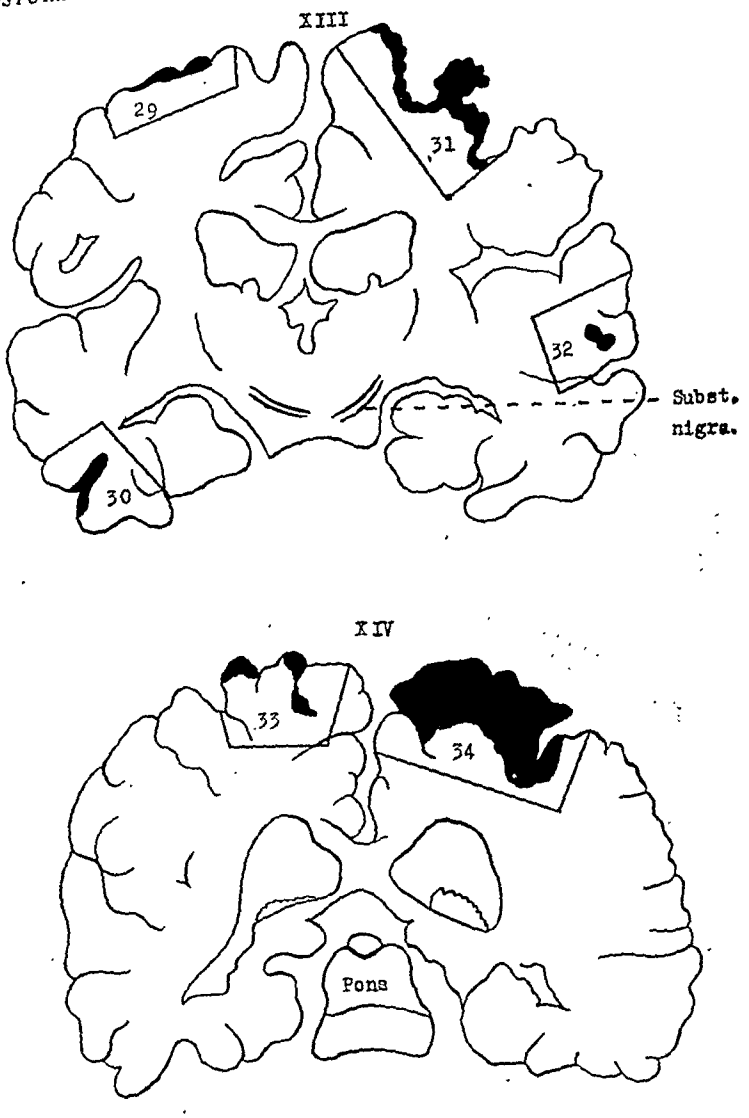
In addition to the malacias in the cortex, the basal ganglia on both sides contain several similar ones, as does the right capsula interna.

The exact locality of the malacias is seen on the attached orthodiagrams of the sections through the brain. The parts histologically examined are numbered on the diagrams. For the sake of brevity and lucidity the results of the histologic examination are presented in tables. The frequency of thrombotic vessels, the distribution and size of the malacias and the intensity of the cell infiltration have been estimated and graded (+), + and ++. The approximate age of the malacias is stated in the last column in the table. As regards the malacias the age of which has been denoted by »years», it is not possible, on the basis of the histologic picture, to determine whether they are 1, 2 or 3 years old, or still older.




## Histopathologic examination.

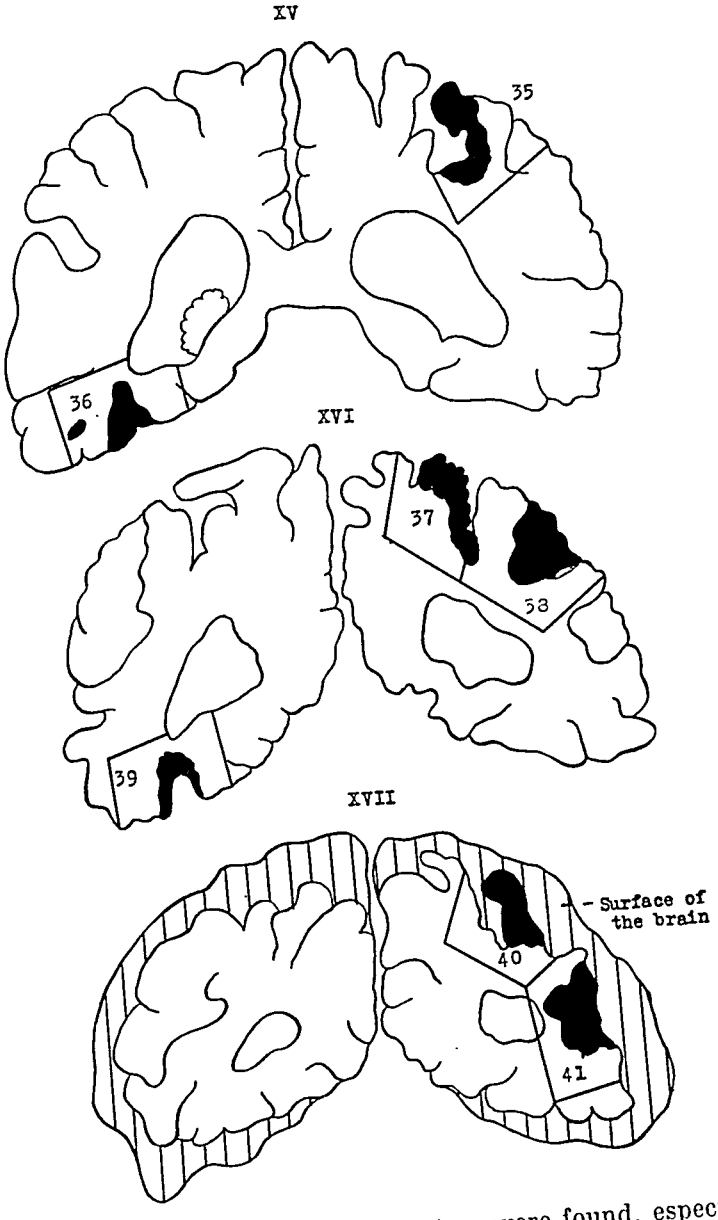
*Cerebellum and cerebrum.* The histologic picture of the encephalomalacias is in the main what would be expected from the macroscopic picture: Mainly old malacias with a more or less complete destruction of the grey but also of the white layers, moderate infiltration by macrophages containing hemosiderin and also solitary cells containing fatty granules and round cells. In places there are signs of beginning formation of cysts. In the margin of the surrounding brain parenchyma there is a considerable neurogliar proliferation. In some places there are small glial scars without any inflammatory changes. The cortex contains numerous so-called laminary malacias, Lam. I especially, and sometimes also Lam. II being comparatively normal.




The coarser as well as the finer arteries show but slight arteriosclerotic changes, generally only a very light and diffuse thickening of the wall. No arteriolosclerosis demonstrable.

In all sections there are very striking vascular changes of another kind, viz. recent and old thrombi, often with a pronounced recanalization. The newfound canals through the thrombi are frequently strikingly wide as compared with the diameter of the vessel itself and the connective tissue sparse. When there are several new channels through a thrombus the canals often have very much the same diameter and the cross-section of the vessel thus has the shape of a clover leaf. A comparatively thin and but slightly changed vascular wall thus encloses several fresh paths for the blood through the old thrombus. Cf. figs. 1 and 2. Nowhere have inflammatory changes in the walls of the vessels been found nor any signs of thrombangitis obliterans Buerger.

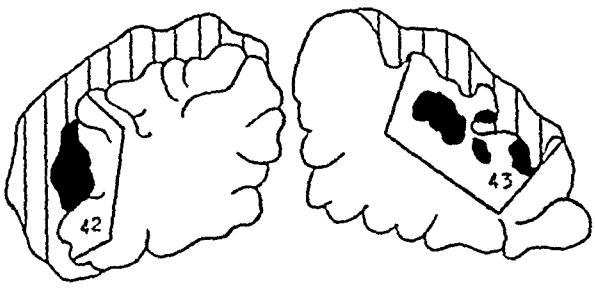
*Spinal cord.* In a number of sections from the cervical, thoracic and

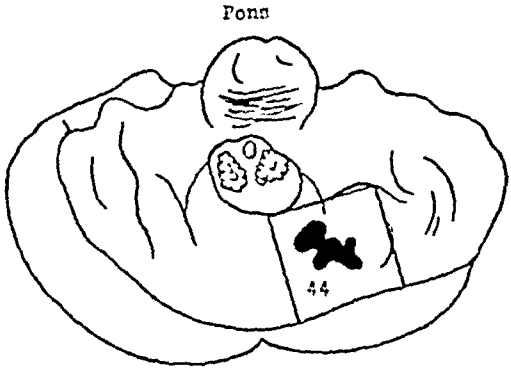



lumbar cord small demyelinization centres were found, especially in the spinal nerves but also in the posterior roots. No inflammatory changes. No malacias in the grey substance nor any thrombi in the spinal vessels.

*Kidneys.* Marked arterio-arteriolosclerosis with partly confluent scars in the cortex. The coarser arteries show pronounced arteriosclerosis of Jores' type. The arterioles are homogenitized and hyalinized. In sections stained acc. to Ladewig it was possible only in a couple of arterioles to demonstrate fibrinoid degeneration of the vascular wall. In the scars in the cortex the glomeruli are frequently transformed into hyalinized balls of connective tissue, but in the better preserved parts the glomeruli show no marked pathologic changes. No signs of glomerulonephritis.

XVIII




*Heart.* In the examined parts of the left ventricle there are large and small old scars. No fresh myomalacias are seen. In several places the lumen of the single branches of the coronary arteries is divided into two or three channels, results of the recanalization of old thrombi. No fresh thrombi found nor any inflammatory changes.

Sections through the mitral valves show the typical picture of an old healed and of recurrent verrucous endocarditis, resembling a rheumatic process. The tissue of the valves consists of fibrous, hyalinized connective tissue, poor in cells and containing small blood vessels. On the surface there are comparatively fresh thrombi, rich in fibrin, with beginning organization in the deeper layers. No leukocytic reaction.

*Summary:* The autopsy thus reveals a case of chronic and recurrent verrucous endocarditis, closely resembling one of rheumatic origin.

The myocardium contains numerous scattered, large and small old scars of connective tissue.

The kidneys show the picture of a moderately pronounced arterio-arteriolosclerosis, explaining the patients hypertension.

The central nervous system is pierced, apparently in no special order, by a very large number of large and small, mainly old encephalomalacias.

Judging by the organs examined there is comparatively slight general arteriosclerosis.

The most interesting feature of the case is the demonstration of multiple, frequently organized, recanalized thrombi in large as well as small arterial branches both in the myocardium and, especially, in the central nervous system. The absence of noteworthy arteriosclerotic vascular changes in these organs combined with the presence of a returning verrucous endocarditis in the mitral orifice make it appear very probable that the multiple thrombi and the encephalomalacias caused by them are of embolic origin.

## Discussion.

The litterature on postural hypotension offers very little information about the pathologic-anatomic basis of the condition, and we have found only two cases in which autopsy has been performed. One is a typical Addison case of tuberculous origin (20) and the other is one of the cases described by Bradbury and Eggleston (19). In the latter case no examination was made of the central nervous system. The chief post-mortem finding was chronic myocarditis with dilation of the heart.

Ellis and Haynes (21) have published four cases of postural hypotension with spinal cord lesions such as locomotor ataxia, syringomyelia and haematomyelia. Strisower (38) studied the blood pressure in 17 cases of locomotor ataxia and observed a pronounced orthostatic lowering of the blood pressure in 9 of those cases. He did not report on the pulse rate during the blood pressure fall. Capps and de Takáts have described two cases of postural hypotension after bilateral denervation of the carotic sinus (39).

In view of the fact that in postural hypotension there are signs of extensive lesions of the vegetative nervous system, several authors have assumed that cerebral injuries may be the cause of the syndrome. No pathologic-anatomic examination confirming this assumption has been found in the litterature.

In the case here described the clinical picture is dominated by cerebellar and cerebral symtoms. There is no reason for assuming that the primary basic diseases — nephrosclerosis and chronic endocarditis — were the direct cause of the postural hypotension. This no doubt has to be connected up with the encephalomalacias. Due

to so many different parts of the central nervous system being affected, it is not possible to localize the encephalomalacias responsible for the syndrome.

It appears possible to explain the patients' initial symtoms in the spring of 1935 by the old encephalomalacia in prep. 19, located in the right internal capsule. The acute symtoms in Aug., 1938 may very probably be due to the lesion in the cerebellum, prep. 44.

Further, the weakness of the right leg may have been caused by the malacia in prep. 21, and the steadily declining vision of the left eye may, at least partly, be attributed to the multiple injuries in the two occipital lobes (prep. 41, 42, 43).

The most marked signs of postural hypotension appeared about one month prior to the death of the patient and it is thus of interest to study the localization of the malacias the age of which has been estimated, with the aid of the histological picture, a month or so. As seen from the table and the orthodiagrams, these malacias (prep. 3, 4, 7, 35, 36, 37, 42) are all situated in the cortex of the cerebrum, generally in the lateral parts of the hemispheres.

## Summary.

In connection with a survey of the orthostatic regulation of the blood pressure under physiologic conditions attention is directed to the information supplied by the study of sympathectomized patients regarding the part played by the vessels in the splanchnic area in the regulation of the blood pressure in a standing position.

Stress is placed upon the fact that in order to understand the disturbances of the orthostatic regulation of blood pressure it is necessary to distinguish between the two important syndromes —arterial orthostatic anaemia and postural hypotension — in which such disturbances occur.

A clinical and pathologic-anatomical study is presented of a man, age 48, who during five years displayed symptoms of repeated cerebral injuries. The patient had hypertension and other signs of nephrosclerosis. Towards the end of life there developed typical postural hypotension of which a clinical study was made. In the post mortem it was found that the patient had suffered not only from nephrosclerosis but also from a chronic verrucous endocarditis resembling the rheumatic type which had given rise to multiple

encephalomalacias. The age and localization of the encephalomalacias have been analysed, and likewise their assumed connection with the patient's symptoms.

In the literature on postural hypotension it has repeatedly been assumed that injuries to the central nervous system are the cause of the syndrome. To our knowledge this is the first case of this syndrome in which injuries to the central nervous system have been subjected to a pathologic-anatomic study.

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(From the Maria Hospital, Helsingfors, medical department. Chief: Professor Fredrik Saltzman).

# The reticulocytes at the formation of rouleaux and the sedimentation reaction.

By

MAJ-LIS ÅBERG.

(Submitted for publication May 5th, 1942).

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The vitally stainable erythrocytes, the reticulocytes, are regarded in general as young red blood corpuscles which pass through the last phase of their evolution. In a completely healthy person, the number of reticulocytes in the peripheral blood is very low, under 1 %, but after a considerable loss of blood, for example, or in liver therapy in a patient suffering from pernicious anaemia, their percentage can rise to 50 %, and sometimes even higher. This is the first sign of a rapid new formation of red blood corpuscles.

In a blood preparation supravitally stained with brilliant cresyl blue, the reticulocytes can be recognised by their characteristic blue-tinted, net-like structure. The appearance of this structure can vary somewhat, depending on the amount of vitally stainable substance that the corpuscle contains. This amount, again, is determined by the age and maturity respectively of the reticulocyte. A number of investigators (Seyfarth, Hirschfeld and Moldawsky) have divided the reticulocytes into three groups. Perhaps the most usual division is that of Heilmeyer, into four:

Group 0 contains the most immature cells, the nucleus-carrying red corpuscles; group I reticulocytes with a compact, nucleus-like lump generally situated in the centre of the cell; group II a maturer

form with a distinct net of coarse meshes; group III fragments of the net, rods or dots scattered in the cell; group IV small dots, mainly in the cell's periphery. These different groups represent different degrees of development in the reticulocyte, and the percentage figure of the different groups can give a good idea of the blood's regeneration. Forssell has shown that when the regeneration of the red corpuscles is slow, quite mature reticulocytes from groups III and IV usually abound in most number, while those from groups I and II predominate in a rapidly setting in reticulocytosis.

Trachtenberg has drawn up a table (Table 1.) showing the approximate amount of reticulocytes in normal blood divided up into four groups. The figures give the number of reticulocytes per 1000 red blood corpuscles.

Table 1.

| | | |
|---|---|---|
| Group 0 | — | |
| Group I | 0— 1.0 ‰ | Average 0.09 ‰ |
| Group II | 0— 2.5 ‰ | » 0.9 ‰ |
| Group III | 0— 4.0 ‰ | » 1.5 ‰ |
| Group IV | 0—13.0 ‰ | » 5.5 ‰ |

This grouping provides a certain criterion for the new formation of erythrocytes. The boundaries between the different groups are very indefinite; groups II and III in particular are not easy to separate. Group IV appears more plainly in vitally stained smeared preparations than in vitally stained coverglass preparations.

As a basis for my own investigations, I have carried out reticulocyte differentiations in 50 normal cases. As this method is fairly subjective, a relative displacement in different investigators' normal values may exist. My normal values, which are shown in Table 2, differ from those of Trachtenberg, in that group III is somewhat larger than group IV.

Table 2.

| | | |
|---|---|---|
| Group 0 | — | |
| Group I | 0— 1.0 ‰ | Average 0.1 ‰ |
| Group II | 0— 5.0 ‰ | » 0.8 ‰ |
| Group III | 0—11.0 ‰ | » 3.52 ‰ |
| Group IV | 0—10.0 ‰ | » 2.78 ‰ |

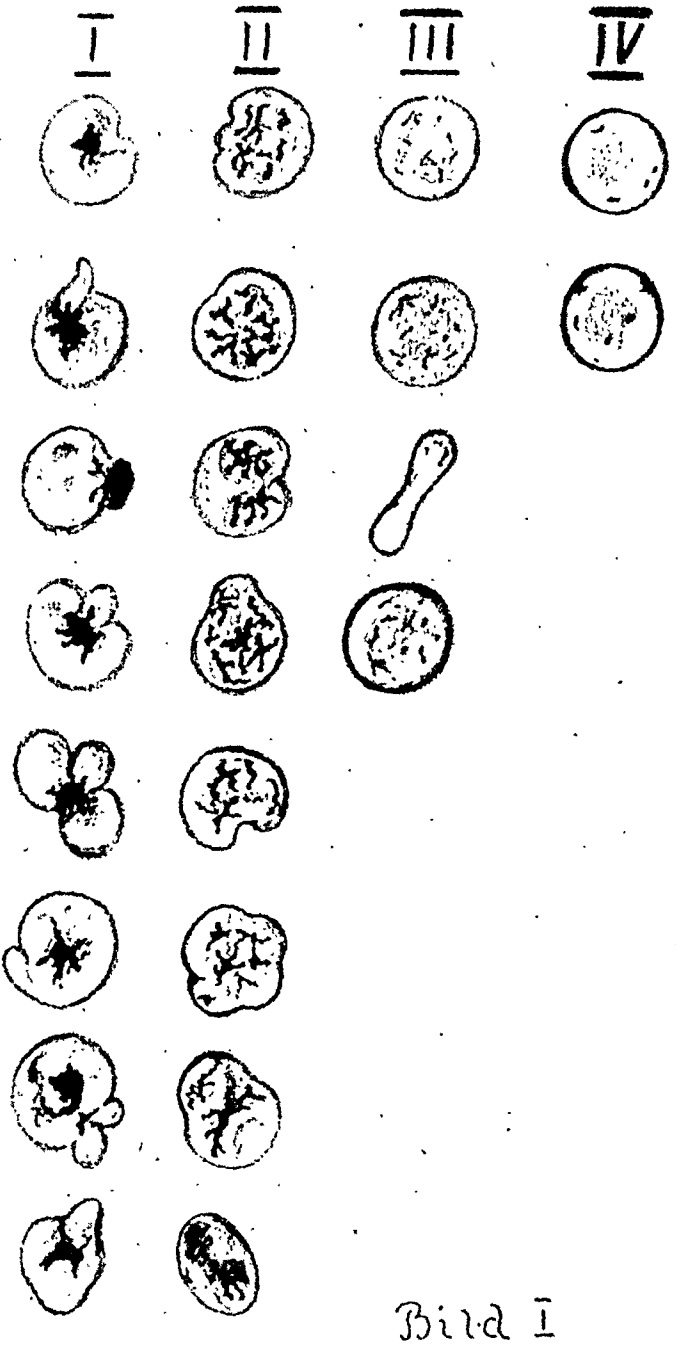



Bild I

Bild I.

While investigating vital blood, Fåhraeus observed oddly shaped red corpuscles, which he has called 'hilus forms'. They have a round-oval shape with an uneven surface and often one or several sharp indentations. In examinations of blood from sedimentation tests, Nurse Lisa Boström found corpuscles most nearly resembling 'knots'. They are highly supravitally stainable. Taking everything into consideration, the hilus forms and the bundles are probably identical. Gripwall has subsequently studied these hilus cells in more detail, specially in hereditary haemolitic jaundice and pernicious anaemia. In both diseases there is a so called veiled sediment present; i. e., the boundary between the clear layer and the corpuscle column is more or less indistinct. Between them can be seen a cloudy layer, the veil. In this there was an abundance of hilus forms or knots. Valentine has also mentioned deformed, vitally stainable cells of this kind, and taken them to be reticulocytes. At the formation of rouleaux, the hilus forms remain outside the aggregate in the same way as the leucocytes and the thrombocytes. In a paper written parallel with my investigations, Sievers has stated that they do not agglutinate at a determination of the blood group, either. According to his results, the predominating number of reticulocytes, which remain outside the agglutination, belong to group I. As soon as the reticulocytes have reached a certain maturity, they react in the same way as the mature erythrocytes.

On account of the gradual transition from group to group which is taking place, the division of reticulocytes must to some extent be influenced subjectively. Partly on this account, and partly on account of the different designations — hilus forms, knots, reticulocytes — which exist, and which as a whole or in part apply to the same kind of erythrocytes, I reproduce below a figure showing how I have divided up the reticulocytes.

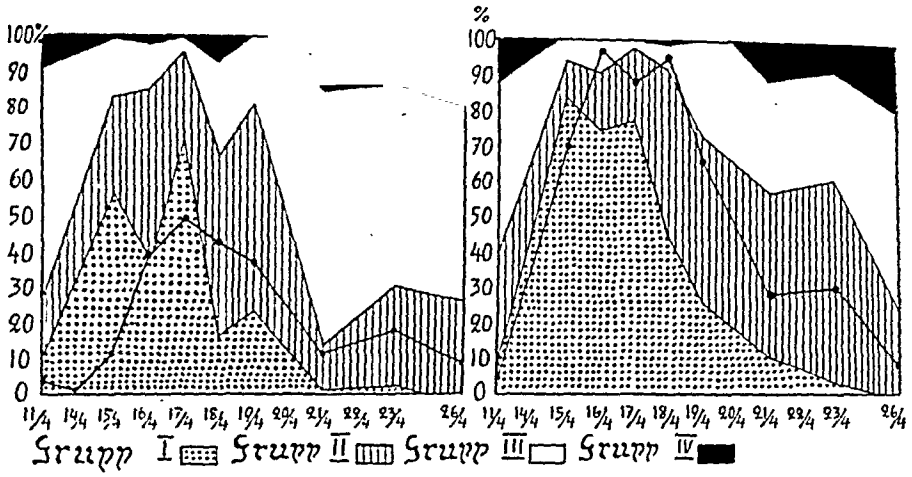
My intention now was to investigate more closely the difference between the reticulocytes in the blood and those outside the aggregate at the formation of rouleaux. To this end, a reticulocyte count was made in the blood in the usual way, and also in blood mixed with serum from the same blood group as that of the experiment subject — as a rule, his own serum.

*Technique:* A drop of blood from the finger was smeared out with a fine glass rod on a fairly strongly stained object glass (3—4 drops of 1 % alcoholic brilliant cresyl blue solution are dropped on the

object glass, allowed to dry, and are rubbed lightly with a dab.) A largish coverglass is put on top, and the sample allowed to stand about 2 minutes, after which the coverglass is carefully removed and the stained blood drop is spread into an ordinary smeared preparation. Left to dry quickly in the air. The reticulocytes are counted per 1000 erythrocytes. Immersion lense and slightly shaded light. The reticulocytes in the groups mentioned earlier are differentiated at the same time.

For the sample with rouleaux formation, a drop of blood from the finger is taken on a similarly stained object glass and mixed with the staining matter as in the previous test, after which an equally large drop of well centrifuged serum from the experiment subject is added. Both drops are well mixed with the glass rod, a largish coverglass is adjusted. After about 5 minutes, the rouleaux aggregat has formed; the reticulocytes outside are counted and differentiated as previously. 1000 erythrocytes are counted. Preparations showing damaged erythrocytes — spherocytes, or having a shape like a spiked club — are thrown away. It may here be pointed out that spiked-club-shaped reticulocytes of the first or second degree seldom occur.

*Material:* In a series of normal cases where the reticulocyte percentage in the blood varied between 0.3—1.0, the experiment with rouleaux formation yielded reticulocytes outside the aggregate to a value of 0.3—1.2 %. This difference must be regarded as falling within the limits of possible errors in counting. When the reticulocyte values were somewhat higher, 3.0—10.0 %, the corresponding figure for the reticulocytes outside the aggregate was 2.0—12.0 %. At higher reticulocyte values after slow reticulocytosis, the difference was already somewhat greater. The reticulocyte percentage in a patient with haemorrhagic anaemia was, in the blood, 35, and outside the rouleaux formation, 39.4. Two days later, the same patient had 20.5 % reticulocytes in the blood, and 28.0 % outside the aggregate. These variations are probably already beyond the limits of possible errors in counting. However, as the differences were, in this case also, relatively small, I investigated further cases where the reticulocyte percentage was rather higher still, and where above all the reticulocyte increase took place much more quickly. The 3 patients concerned all suffered from pernicious anaemia. When choosing the material, consideration was paid to the fact that




Kurves I and II.

younger forms of the reticulocytes could be expected in these cases than in the previous ones. Curves I and refer to one of these 3 cases; the two others showed in the main the same situation. (This case is identical with Case 6 in Sievers' paper).

Curve I shows the typical reticulocyte crisis in the blood, while Curve II shows the reticulocyte curve outside rouleaux formation. In each, the reticulocytes percentage figure can be read off on the ordinate and the date the sample was taken on the abscissa. The unbroken line gives the reticulocyte percentage. The differently marked areas represent the four groups of reticulocytes. It can be seen from the curves that as long as groups I and II predominate, the reticulocyte curve at the aggregation experiments remains higher than that in the blood. This suggests that *reticulocytes from groups I and II take no part, or at most very little, in the rouleaux formation, whereas the reticulocytes from groups III and IV do to a considerably greater degree.*

The rouleaux formation and the sedimentation reaction are to a certain extent interdependent. For this reason, the sediment offered itself at once as a starting-point for continued investigations. Fåhraeus, Gripwall and Boström have all studied the uppermost layer of the sediment and all found more or less profuse hilus forms or bundles. In particular the veil in the veiled sediments consists largely, in a number of cases, of these hilus forms. A more detailed analysis of the presence of the reticulocytes in the different layers in the sedimentation tube is intended to elucidate more clearly, and

in a more comprehensive manner, the recently described phenomena at the formation into rouleaux. The method was as follows:

Sample 1. The reticulocytes in the blood were counted and differentiated in the way described earlier.

Sample 2. An ordinary sample was taken with 3.8 % sodium citrate solution for sedimentation reaction. It was put in a stand and left to sediment for 2 hours. A drop of the colourless, slightly opalescent liquid immediately above the corpuscle column was taken with a Pasteur pipette. The drop was placed on a stained object glass, mixed with the staining matter and spread out as described earlier; this was to avoid aggregation when counting. The erythrocytes were few, and in the thinner preparation they showed a great tendency to form rouleaux. In the majority of cases, however, the reticulocytes were first counted and differentiated in the moist preparation, before it was spread into a smeared preparation. In the moist preparations, all hilus forms with marked protuberances and dark indentation were relegated to group I, less pronounced hilus forms with net structure to group II. The reticulocytes in wet preparation and in dry smeared preparation are given in Table 3. *It appears as though the hilus forms and the reticulocytes from grops I and II were somewhat similar in respect of those properties connected with the sedimentation rate.* Readers may here be referred to Sievers' observations touching the appearance of group-specific agglutinogen within the different reticulocyte groups.

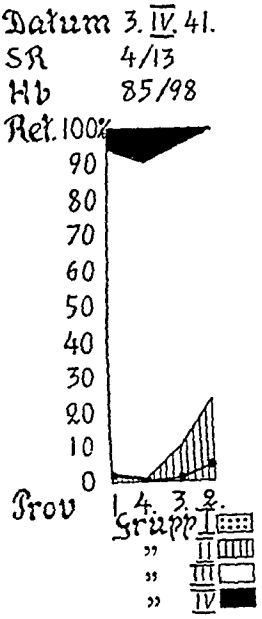
Table 3.

| Wet preparation. | | Dry smeared preparation. | |
|---|---|---|---|
| Reticulocytes ..... | 44.6 % | Reticulocytes | 48.0 % |
| Pronounced hilus forms | 75 % | Group I .... | 72 % |
| Less pronounced » | 24 % | Group II .... | 27 % |
| Group III » | 1 % | Group III.... | 1 % |

Sample 3. A reticulocyte preparation was taken in the same way with a Pasteur pipette from the actual boundary layer between the colourless liquid column and the corpuscle column. Here it was possible to see under the microscope a faint red thinge in the drop in the pipette. If the sediment was a so-called veiled one, sample 3 was taken in the middle of the veil. The preparation was counted and differentiated in the same way as Sample 2.

Sample 4. The last sample was taken from the bottom layer of the corpuscle column. When the sedimentation pipette was taken away, the first drop of blood was allowed to run out, and a reticulocyte preparation was made from the next one, which was stained and counted like the preceding.

Curve III shows samples from a person with a normal number of reticulocytes. As in the preceding curves, the reticulocyte percentage and that of the different groups is read off on the ordinate. The

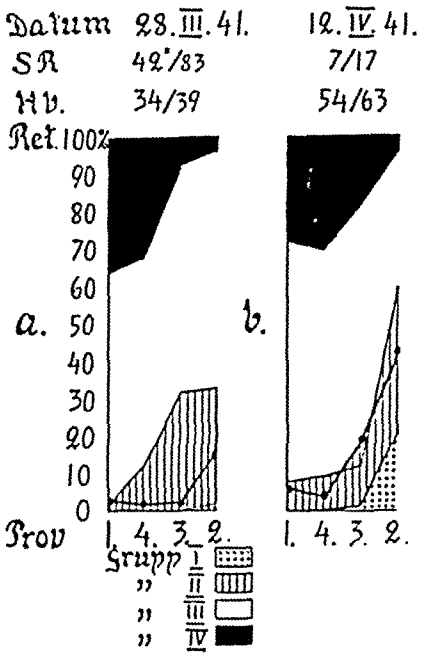



Kurve III.

unbroken line gives the reticulocyte percentage in the different samples, the variously marked areas show the four reticulocyte groups. In this curve, the divergencies are not pronounced. Group I is missing altogether and does not even appear in Sample 2. Group II is very scantily represented. Groups III and IV predominate.

Another situation is already seen from Curves IV, a and b. The curves refer to a case of haemorrhagic anaemia. The first investigation was made on the patient's admittance (Curve IV a), and the second some weeks later, when the reticulocyte percentage was at its height (Curve IV b). IV b in particular shows a distinct displacement in the reticulocyte curve, in that Sample 2 shows a far higher reticulocyte percentage than Sample 1. In Sample 2, group I rises to 20 %, although no reticulocytes from this group could be

shown with certainty in Sample 1. The reticulocyte percentage sank rapidly in the following Sample 3, and there the reticulocyte percentage for group 1 rose only to 1 %, to disappear completely in Sample 4. Here the reticulocyte percentage was thus less than the one in Sample 1. The remaining groups II, III and IV showed no very great variations. A comparison between Curves IV a and IV b reveals dissimilarities in the reticulocyte picture during different phases in the course of the anaemia and the corpuscle regeneration.



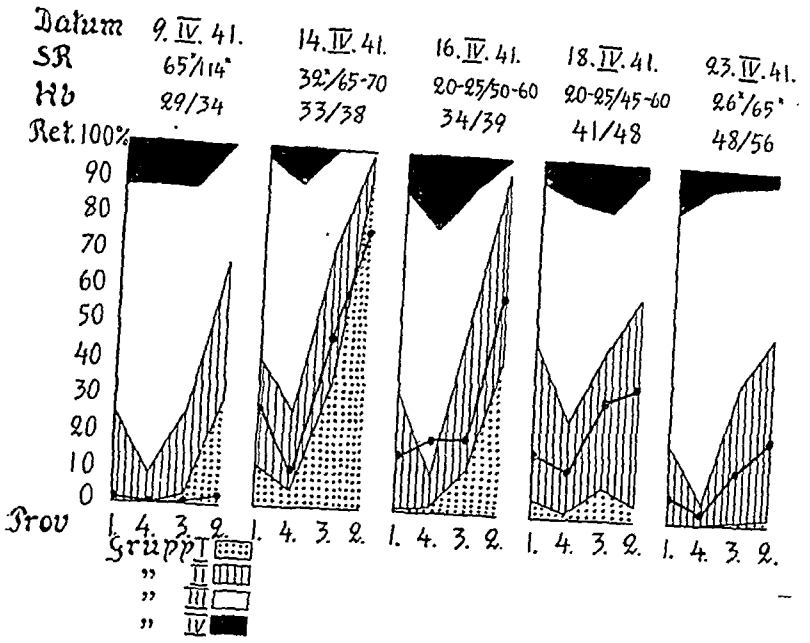

Kurves IV, a and b.

Curve V shows the variations between the different samples even better.

In this series of samples from a patient with pernicious anaemia, the first was taken before the reticulocyte crisis, the second at its climax, and the three later ones as it was subsiding. Above the respective curves, the date the sample was taken, the value of the sedimentation reaction and the haemoglobin content, are noted. The sediment was a typical veiled one.

*This experiment goes to show that the reticulocytes from groups I and II in the sedimentation tube mainly keep above the red blood corpuscle column, while those from groups III and IV seem to tally with the ordinary erythrocytes.*

It is striking that the different kinds of reticulocytes show the




Kurve V.

same situation on the one hand at the rouleaux formation and on the other at the sedimentation of the blood. Another noteworthy fact is that, as Sievers has shown, a similar phenomenon appears at the isoagglutination of the blood corpuscles. Yet we know that agglutination and rouleaux formation are two widely different phenomena (see Fåhraeus, Schiff, Bergenhem, Sievers, for further details).

Gripwall has very thoroughly discussed the question of why the reticulocytes show a lower sedimentation rate than the mature red corpuscles. On the strength of his investigations he considers himself able to prove that this is not due to a lower specific weight in the reticulocytes, but instead to their small tendency to form an aggregate. He does not say what this small tendency is due to. As it seems as though the lowered sedimentation rate and the lowered tendency to aggregate formation is a property primarily belonging to the immaturest reticulocytes — those of groups I and II, and as the reticulocytes from these two groups exhibit the greatest irregularities in their shape and the greatest divergencies from that of the mature erythrocytes, it is plausible to see in this shape of theirs an important cause to the peculiarity we have been dealing with at the sedimentation and rouleaux formation.

## Summary.

The foregoing investigations go to show:

1) that the reticulocytes from groups I and II have no part, or very little, in the rouleaux formation, while the reticulocytes from groups III and IV take a considerably larger part in it,

2) that the reticulocytes from groups I and II keep mainly above the red blood corpuscle column in the sedimentation tube, while groups III and IV seem to tally with the mature erythrocytes,

3) that the hilus forms, bundles and reticulocytes from groups I and II are somewhat identical,

4) that consequently the shape of the red blood corpuscles can, judging from everything, have an effect on their sedimentation rate.

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